Risk of incident vascular disease in patients with gout: an observational study in the Clinical Practice Research Datalink

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Abstract

Gout is the most prevalent inflammatory arthritis, predominantly managed in primary care. Both hyperuricaemia (the biochemical precursor to gout) and other inflammatory arthritides, e.g. rheumatoid arthritis, have been shown to increase risk of vascular disease. This thesis aims to investigate the risk of incident cardiovascular, cerebrovascular and peripheral vascular disease in primary care gout patients.

A systematic review identified 17 studies investigating gout and vascular diseases. Meta-analysis showed increased mortality from all cardiovascular and coronary heart disease. Increased incidence of, but not mortality from myocardial infarction was found. Few studies investigated the association between gout and cerebrovascular or peripheral vascular disease.

A retrospective cohort study used data from the Clinical Practice Research Datalink to examine the risk of incident cardiovascular, cerebrovascular and peripheral vascular disease in 8386 gout patients and 39766 age-, gender- and practice-matched controls, in the ten years following diagnosis of gout (or matched date) using Cox proportional hazards and multilevel discrete-time event history analysis. Risk was also investigated by gender and with follow-up limited to one, two and five years. The effect of exposure to drugs used to treat both gout and vascular risk factors on the magnitude of risk was examined using a cohort and nested case-control study design.

The strongest association identified was between gout and peripheral vascular disease. Women with gout had the greatest excess vascular risk and experienced

a wider range of vascular events. Exposure to drugs used to manage vascular risk factors was associated with increased likelihood of a vascular event, but use of gout treatments such as allopurinol did not influence incident vascular risk.

This suggests that gout patients, particularly women, should have screening for and aggressive management of vascular risk factors, although as conventional approaches may be insufficient, further research is required to establish the optimum risk reduction strategy.

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I would like to dedicate this thesis to my lovely family, my husband Sam, my daughter Megan, and my parents Paul and Chris, without whom none of this would have been possible. Their support over the last three years has been unwavering as always, and I am extremely grateful to you all.

Glossary

ACE	Angiotensin-Converting Enzyme
ACR	American College of Rheumatologist
ACS	Acute Coronary Syndrome
AD	Autosomal Dominant
ADP	Adenosine Diphosphate
AHR	Adjusted Hazard Ratio
AIR	Annual incidence rate
AMI	Acute Myocardial Infarction
AMP	Adenosine Monophosphate
AOR	Adjusted Odds Ratio
AR	Autosomal Recessive
AS	Ankylosing Spondylitis
ASC	Apoptosis-Associated Speck-Like Protein
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BP	Blood Pressure

BSR	British Society of Rheumatology
cAMP	Cyclic-Adenosine Monophosphate
CCB	Calcium Channel Blocker
CCI	Charlson Co-morbidity Index
CHD	Coronary Heart Disease
CHR	Crude Hazard Ratio
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COR	Crude Odds Ratio
COX	Cyclo-Oxygenase
CPH	Cox Proportional Hazards
CPPD	Calcium Pyrophosphate Dihydrate
CPRD	Clinical Practice Research Datalink
CRP	C-Reactive Protein
CV	Cardiovascular
CVA	Cerebrovascular Accident

CVD	Cerebrovascular Disease
DDD	Defined Daily Dose
D&L	DerSimonian & Laird
DM	Diabetes Mellitus
DMARD	Disease Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
EHR	Electronic Health Records
EMBASE	Excerpta Medical Database
ESRD	End-Stage Renal Disease
EULAR	European League Against Rheumatism
FeUA	Fractional excretion of Uric Acid
FH	Family History
GLUT	Glucose Transporter
GMP	Guanosine Monophosphate
GP	General Practitioner
GPRD	General Practice Research Datalink
HDL	High-Density Lipoprotein
HES	Hospital Episode Statistics

HLD	Hyperlipidaemia
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPRT	Hypoxanthine Guanine Phosphoribosyl Transferase
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
H(t)	Hazard Function
HTN	Hypertension
ICD	International Classification of Diseases
ICHPPC	International Classification of Health Problems in Primary Care
IHD	Ischaemic Heart Disease
IL	Interleukin
IMP	Inosine Monophosphate
IQR	Inter-quartile Range
IR	Insulin Resistance
JH	Johns Hopkins Hospital
LDL	Low-Density Lipoprotein
LnHR	Natural Logarithm of the Hazard Ratio
LR	Likelihood Ratio

MDtEHA	Multilevel Discrete-time Event History Analysis
MedLine	Medical literature analysis and retrieval system Online
MeSH	Medical Subject Heading
MI	Myocardial Infarction
MH	Meharry Hopkins Hospital
MPR	Medication Possession Ratio
MR-FIT	Multiple Risk Factor Intervention Trial
MSU	Monosodium Urate
MTP	Meta-tarso Phalangeal
NAD	Nicotinamide Adenine Dinucleotide
NADH	Nicotinamide Adenine Dinucleotide (reduced)
NALP	NACHT, LRR and Pyrin domain-containing Protein
NHS	National Health Service
NLR	NOD-like Receptors
NO	Nitric Oxide
NOS	Newcastle-Ottawa Scale
NS	Not Statistically Significant
NSAID	Non-steroidal Anti-Inflammatory Drugs

OA	Osteoarthritis
OAT	Organic Anion Transporter
OR	Odds Ratio
ORLS	Oxford Record Linkage Study
OXMIS	Oxford Medical Information Systems
PCR	Polymerase Chain Reaction
PMR	Polymyalgia Rheumatica
PVD	Peripheral Vascular Disease
PY	Patient Years
RA	Rheumatoid Arthritis
RAS	Renin-Angiotensin System
RCGP	Royal College of General Practitioners
RCT	Randomised Controlled Trial
ROS	Reactive Oxygen Species
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error
SLE	Systemic Lupus Erythematosus

SMC	Smooth Muscle Cell
SpA	Spondyloarthropathy
S(t)	Survival function
SUA	Serum Uric Acid
THIN	The Health Improvement Network
TIA	Transient Ischaemic Attack
TNF	Tumour Necrosis Factor
UC	Ulcerative Colitis
UK	United Kingdom
ULT	Urate Lowering Therapy
URAT1	Urate Transporter 1
USA	United States of America
WHO	World Health Organisation
XD	X-linked Dominant
XDH	Xanthine Dehydrogenase
XO	Xanthine Oxidase

Chapter 1: Background

1.1 Overview

This chapter summarises the important features of gout considering historical, epidemiological and clinical features.

1.2 History

The clinical condition of gouty arthritis was first described by Hippocrates in the 5th century BC, however, archaeologists have identified evidence of deposits of uric acid in the joints of mummified Egyptians dating from approximately 4000 years ago.

Hippocrates referred to gout as the “unwalkable disease” and observed it was the “arthritis of the rich” in contrast to rheumatism which he considered the “arthritis of the poor”. The writings of Hippocrates provided the earliest epidemiological observations on gout:

> ‘eunuchs do not take the gout, nor become bald, a woman does not take the gout, unless her menses be stopped, a youth does not get gout before sexual intercourse, in gouty affections, inflammation subsides within 40 days, gouty affections become active in spring and in autumn,’ (Adams, 1849)

Much of the historical terminology and context surrounding gout may be explained by Greek legends known to Hippocrates and his contemporaries, such as the story that the goddess Podagre was the product of the seduction of Aphrodite by

Dionysus, the Greek god of wine. (Rodnan, 1965) The Roman physician Galen was of Greek descent and was also thought to have expressed the view that “gout is the daughter of Bacchus,” Bacchus being the Roman name for Dionysus, god of wine. (Gaebel, 1983) Although gout is described relatively frequently in Roman writing, particularly by Seneca, advisor to Nero in 1 AD, gout in women was particularly frowned upon as a sign of deeply flawed moral virtue, (Porter & Rousseau, 2000) perhaps because the male preponderance for the condition was considered to mark out any woman afflicted with it as unusual.

It now seems more likely that the link between gout and the “intemperate lifestyle” was due to the process by which the Romans made wine, rather than the quantity of it consumed. The particular technique by which the Romans preserved wine involved mixing it with grape syrup which had been simmered in lead-lined vessels, resulting in high levels of lead within the wine consumed, which in combination with lead from water which ran through lead-lined pipes resulted in excessive levels of ingested lead. (Nriagu, 1983) Lead poisoning has latterly been linked with gout via a mechanism of chronic kidney disease and an impaired renin-angiotensin-aldosterone system. (Nolan & Shaikh, 1992) Emperors Claudius, Nero, Caligula and Tiberius were known to suffer gout, but were also known for their unusual speech and unpredictable behaviours, perhaps representing the neuro-psychiatric sequelae of excessive lead consumption. (Nriagu, 1983) Industrial and occupational exposure to lead, as well as the presence of lead in household paints has also been linked with high prevalence of gout in the 19th century. (Newcombe, 2012)

Perhaps the most famous description of gout is attributed to the physician and gout sufferer Thomas Sydenham.

> "The patient goes to bed and sleeps quietly until about two in the morning when he is awakened by a pain which usually seizes the great toe, but sometimes the heel, the calf of the leg or the ankle. The pain resembles that of a dislocated bone ... and this is immediately succeeded by a chillness, shivering and a slight fever ... the pain ..., which is mild in the beginning ..., grows gradually more violent every hour ... so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein," (Sydenham & Wallis, 1788)

Gout was considered a condition of the higher social classes and was therefore desirable. It was written in the London Times in the 1900's that,

> "The common cold is well named- but the gout seems to instantly raise the patient's social status." (Copeman, 1964)

The term gout, from the Latin "gutta", meaning drop, originated from the belief that health and disease arose from the balance between the four bodily humors (black bile, yellow bile, blood and phlegm), gout being caused by humors falling to the affected body part causing inflammation and swelling. (Copeman, 1964) The Greek word *podagra* or "foot-grabber" refers to the predilection of gout for the foot, in particular the first metatarsophalangeal joint, and dates back to the second century AD. (Porter & Rousseau, 2000)

Antoni van Leeuwenhoek was the first to describe crystals from a gouty tophus seen under a microscope in the late 17th century. Although their chemical

composition was not understood until much later, he described them to be, “long, transparent little particles, many pointed at both ends and about 4 'axes' of the globules in length.” (Porter & Rousseau, 2000) Karl Scheele was the first to isolate uric acid from a renal calculus in the 1700’s, and Wollaston the first to show the presence of urate in aspirate from a gouty tophus from his own ear. (Scheele, 1776; Wollaston, 1797) The work of Sir Alfred Garrod in the 1850’s made perhaps the seminal discovery in the pathogenesis of gout, differentiating those with gouty arthritis from those with rheumatism using the presence of serum hyperuricaemia. (Garrod, 1848) He also developed the “thread test”, the first clinical chemical test undertaken, which used microscopy to view urate crystals in desiccated, acetate-impregnated serum and finally allowed both a diagnostic test and a clear differentiation between gout and rheumatoid arthritis. (Garrod, 1848)

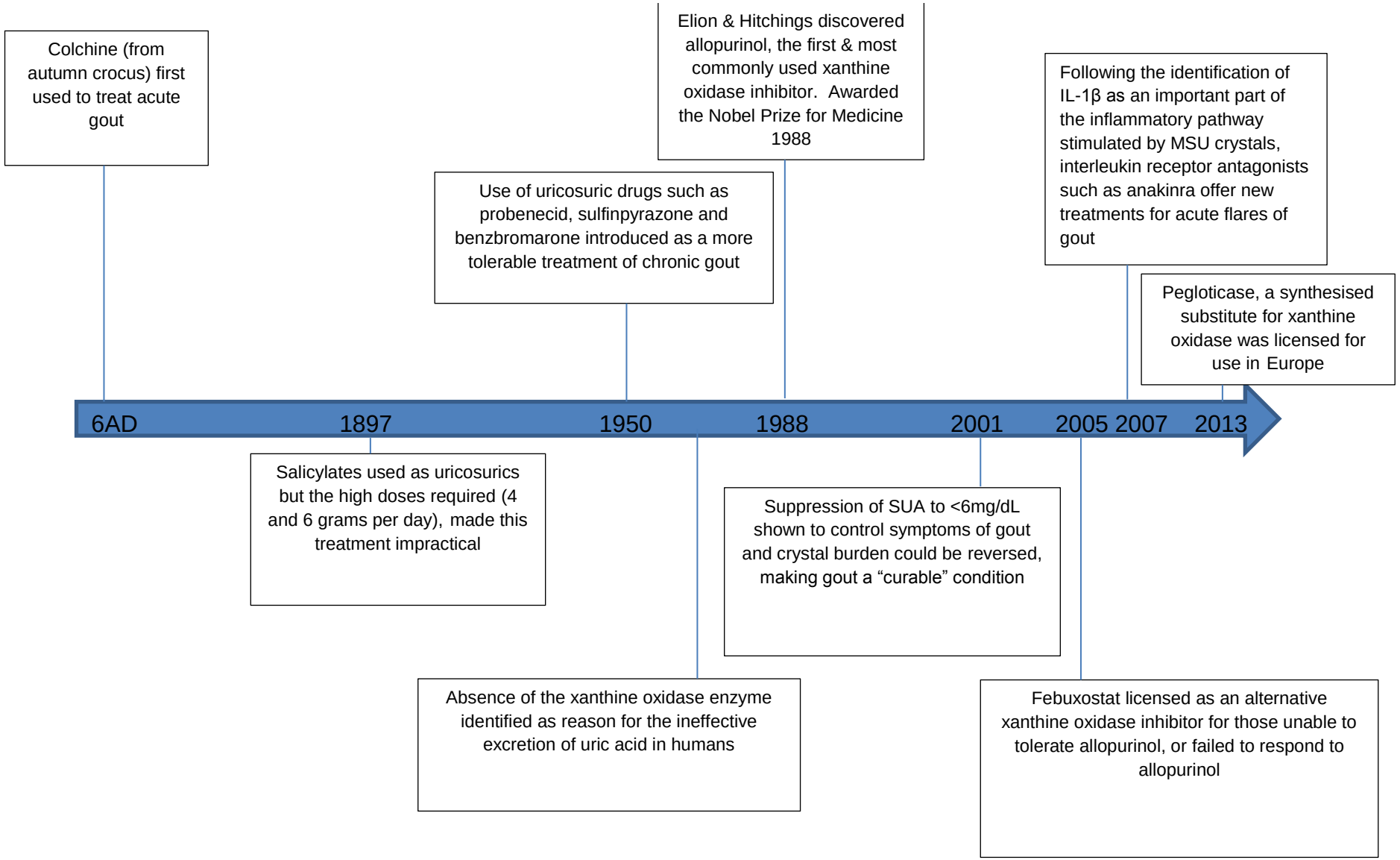
Treatment for acute gout, such as colchicine extracted from autumn crocus, was thought to have been in use as early as the 6th century AD. However, in keeping with its alternative use as a purgative, its use was limited by the associated gastro-intestinal side effects. Sydenham condemned the gastrointestinal side effects of medicines, particularly colchicine, as evidence that it was too poisonous for use. (Copeman, 1964) It was not until a century later that high-dose salicylates were shown to be an effective treatment for acute gout, and despite their limited use due to side effects, paving the way for the modern day use of non-steroidal anti-inflammatory drugs as an alternative to colchicine in acute gout. (Nuki & Simkin, 2006)

Despite the long assumed association between gout and lifestyle, little evidence exists to support this. It was not until 1876 that Sir Alfred Garrod published the

first work suggesting that hyperuricaemia could be controlled by limiting dietary intake of purines. (Garrod, 1876) The first clinical experiments in support of this theory were undertaken between 1894 and 1897, by Haig. (Haig, 1897) Large epidemiological studies examining the impact of various dietary constituents including purines, alcohol, fructose-flavoured soft drinks amongst others, on the incidence of gout, did not begin until the beginning of the 21st century. (Choi et al, 2004a; Choi et al, 2004b; Choi et al, 2007b; Choi & Curhan, 2008; Choi et al, 2009; Choi & Curhan, 2010; Choi et al, 2010)

Prophylactic treatments for gout emerged much later. The important milestones in the treatment of gout are shown in Figure 1.1.

Figure 1.1: Key milestones in the treatment of gout



1.3 Epidemiology

This section will describe the epidemiology of gout including both prevalence and incidence in the UK and worldwide.

1.3.1 Prevalence of gout

1.3.1.1 Prevalence of gout in the UK

Gout is the most prevalent inflammatory arthropathy at 2.5% in the UK, (Kuo et al, 2014) compared to rheumatoid arthritis 0.8%, (Symmons et al, 2002) psoriatic arthritis 0.3%, (Taylor, 2002) and ankylosing spondylitis 40/100,000. (McCormick et al., 1995) Kuo also highlighted the increasing prevalence, estimating this had increased by 63.9% since 1997. (Kuo et al, 2014) Prior to the publication of this most recent study, the prevalence of gout was estimated to be 1.4% in 2005 by two studies using two different databases of primary care electronic patient records (CPRD and the IMS Disease Analyser). (Annemans et al, 2008; Mikuls et al, 2005b) In contrast, a study using the Royal College of General Practitioners (RCGP) Weekly Returns Service, a database of reasons for consultation collected by the RCGP from a network of 100 practices in England and Wales, between 2001 and 2007 estimated the mean prevalence of gout during this period to be much lower at 0.46%. (Elliot et al, 2009) This lower estimate is likely to result from the RCGP Weekly returns service being based on reason for consultation, which since gout is episodic in nature and not all patients consult with every flare, is more representative of the prevalence of consultation for gout rather than that of the disease itself.

1.3.1.2 Prevalence of gout worldwide

The worldwide prevalence of gout is summarised below, grouped by continent, in table 1.1. Within Europe, only Greece has a higher prevalence of gout than the UK, and outside Europe only large developed nations such as Australia and New Zealand and the USA have a higher prevalence of gout than the UK.

Table 1.1: Reported prevalence of gout by continent

Study	Year of publication	Country	Study design	Study population	Definition of gout	Prevalence (%)
Europe						
(Annemans et al, 2008)	2008	Germany	Retrospective cross-sectional primary care electronic medical record database study	4006	At least 2 entries of a gout Read code in primary care record	Period prevalence 2000-2005 1.4
(Anagnostopoulos et al, 2010)	2010	Greece	Prospective cross-sectional population survey	1705	Self report Physician confirmation using ACR criteria	Period prevalence 2007-2008 4.75
(Trifiro et al, 2013)	2013	Italy	Retrospective cross-sectional primary care electronic medical records database study	Not stated	Physician recorded diagnosis of gout	Point prevalence 0.67 in 2005 0.91 in 2009
North and South America						
(Wallace et al, 2004)	2004	USA	Retrospective cross-sectional managed-care administrative database study	Not stated	Physician recorded diagnosis of gout	Point prevalence 0.29 in 1990 0.52 in 1999
(Zhu et al, 2011)	2011	USA	Nationwide population survey (National Health and Nutrition Examination Survey)	5707	Self-report of health professional or physician diagnosed gout	Period prevalence 3.9 in 2007/8
(Pelaez-Ballestas et al, 2011)	2011	Mexico (5 regions)	Cross-sectional survey	19,213	Self-report verified by clinician assessment	Point prevalence 0.3

Study	Year of publication	Country	Study design	Study population	Definition of gout	Prevalence (%)
Asia						
(Nan et al, 2006)	2006	China (Quingdao)	Cross-sectional population based survey	2438	Self-report	Point prevalence 0.36
(Miao et al, 2008)	2008	China (Eastern coastal cities	Cross-sectional population based survey	5003	Self-report validated by ACR criteria	Point prevalence 1.14
(Çakır et al, 2012)	2011	Western Turkey	Cross-sectional population based survey	17,835	Self-report validated by clinical examination	Point prevalence 0.02
(Li et al, 2012)	2012	China	Cross-sectional population-based survey	10,556	Self-report validated by ACR criteria	Point prevalence 0.09
Australasia						
(Klemp et al, 1997)	1997	New Zealand	Cross-sectional population-based survey	657	Clinical examination and ARA survey criteria	Point prevalence 4.7
(Winnard et al, 2012)	2012	New Zealand (Aotearoa)	Cross-sectional study using national administrative health dataset	4,295,296	ICD code for gout in clinical record or record of prescription for allopurinol or colchicine	Point prevalence 2.69 in 2009
(Robinson et al, 2012)	2012	Australia	Systematic review	Not stated, but <28,000 from those where study population is reported	Various	Point prevalence 1.7 in 1995/6
(Smith et al, 2014)	2014	Global	Systematic review	Not stated and cannot be estimated from the paper	ACR survey criteria	Point prevalence 0.08 in 2010

Thus large differences in the prevalence of gout can be seen, even across geographically similar areas. The highest reported prevalence can be seen in New Zealand, Greece and the USA. (Anagnostopoulos et al, 2010; Klemp et al, 1997; Zhu et al, 2011) This may represent differences in genetic or dietary factors, or may simply be the result of using differing definitions of gout (such as self-report versus coded diagnoses in medical records) to estimate prevalence.

Seasonal variation in the prevalence of gout has also been suggested, with peak incidence of both acute attacks and new diagnosis of gout reported during the summer, although the physiological reasons for this trend remain unclear. (Alter et al, 1994; Elliot et al, 2009; Gallerani et al, 1999; McLeod, 1972; Williamson, 1920)

1.3.2 Incidence of Gout

1.3.2.1 Incidence of gout in the UK

The incidence of gout, or the proportion of newly occurring cases of gout within a specified period, had been thought to have remained relatively stable in recent years. (Roddy & Doherty, 2010) However, more recent evidence has suggested that incidence is increasing. (Kuo et al, 2014)

The most recent estimate of incidence examines the period between 1997 and 2012, in the CPRD, the world's largest database of electronic primary care records and reports an overall incidence of gout of 1.8 cases per 1,000 patient years with an average increase in incidence of 1.5% per year. Men had a higher incidence of gout (2.58 cases per 1000 person-years) compared to women (0.99 per 1000 person-years). (Kuo et al, 2014) The CPRD was also used to investigate the

period 1990 to 1999 and reported gout incidence to be at its lowest in 1991, with an incidence of 11.9 cases per 10,000 patient years, and at its highest in 1994, with an incidence of 18.0 cases per 10,000 patient years. The incidence declined to 13.1 cases per 10,000 patient years in 1999. (Mikuls et al, 2005b) The same study also report a higher incidence of gout in males compared with females, with the highest incidence reported in males between the ages of 65-84 years. (Mikuls et al, 2005b) A further study used the RCGP Weekly Returns Service, and investigated the period 1994 to 2007. (Elliot et al, 2009) They reported the mean annual incidence of new gout cases during that period to be 12.4 per 10,000 population, with no evidence of a changing trend. They reported the annual incidence in men to be three times that in women, and increasing incidence with increasing age. (Elliot et al, 2009)

The Health Improvement Network (THIN) database, an alternative database of anonymised electronic primary care records, has also been used to investigate the period between 2000 and 2007. (Cea Soriano et al, 2011) This study estimated the incidence of gout to be 2.68 per 1,000 person years. The incidence of gout was 4.42 (95% CI 4.36 to 4.48) in men and 1.32 (95% CI 1.29 to 1.35) in women per 1,000 person-years and was found to increase with increasing age. (Cea Soriano et al, 2011)

1.3.2.2 Incidence of Gout Worldwide

The studies reporting incidence of gout worldwide are described in Table 1.2

Table 1.2 Incidence of gout worldwide

Study	Year of publication	Country	Study design	Study population	Ascertainment of gout	Incidence
(Roubenoff et al, 1991)	1991	USA	Longitudinal cohort study	1271	Medical record review	1.73 per 1000 PY
(Arromdee et al, 2002)	2002	USA	Retrospective cross-sectional study using electronic medical records	Not stated	ACR survey criteria for gout based on medical record review	AIR 45.0/100,000 1977/8 AIR 62.3/100,000 1995/6
(Bhole et al, 2010)	2010	USA	Prospective cohort study	4427	Self-report of pre-specified criteria strongly suggestive of clinical gout	1.4/1000 PY in women 4.0/1000 PY in men
(Trifiro et al, 2013)	2013	Italy	Retrospective cross-sectional primary care electronic medical records database study	Not stated	Physician recorded diagnosis of gout	0.93/1000 PY in 2005 0.95/1000 PY in 2009
(Maynard et al, 2014)	2013	USA	Longitudinal cohort study	11,963	Self-report	Overall; 0.84/1000 PY (1.5/1000 PY black men; 1.2/1000 in black women; 0.94/1000 PY white men; 0.50/1000 PY in white women

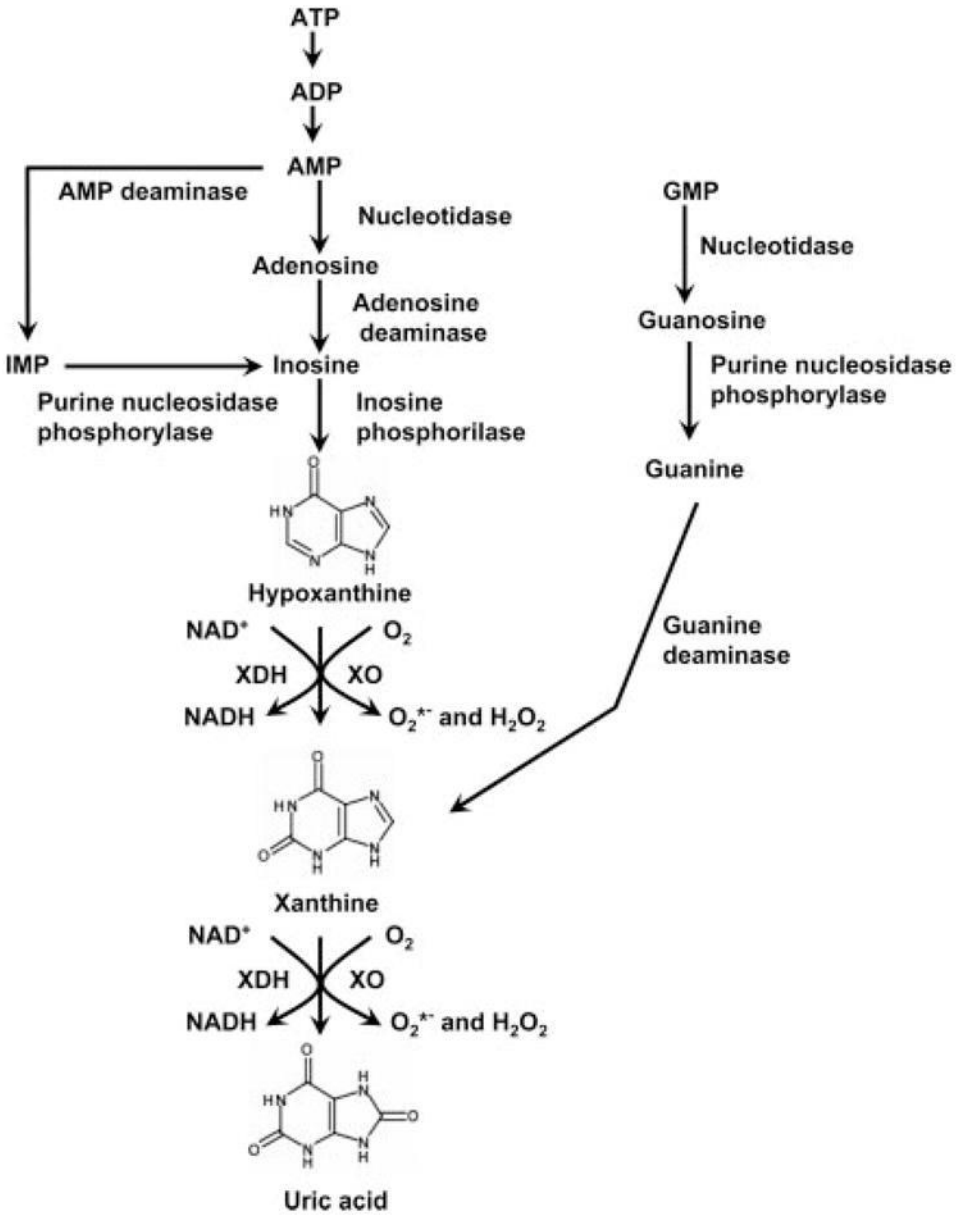
AIR = annual incidence rate; PY= Patient years

1.4 Gout pathophysiology

Gout is the clinical manifestation of deposition of monosodium urate (MSU) crystals in joints and soft tissues. As serum uric acid (SUA) levels rise, eventually the blood becomes saturated with urate, and precipitation of MSU crystals results. These MSU crystals are deposited in the joints and soft tissues, triggering inflammation and painful synovitis.

Uric acid is produced as purines that are both ingested in the diet, and synthesised through tissue degradation, are broken down. This process is illustrated in figure 1.2

Figure 1.2 Uric acid metabolism



Source: (Pacher et al, 2006)

Solubility of uric acid in water is low, and in humans, the evolutionary loss of urate oxidase means that uric acid cannot be converted to the more soluble allantoin, as in other mammals. (Wu et al, 1989) Uric acid homeostasis occurs as production is balanced against its excretion via the renal and gastrointestinal tracts. If this balance is disturbed, levels of serum uric acid begin to rise. In approximately 90%

of cases, this hyperuricaemia is due to impaired renal excretion of urate, with the remaining 10% the result of endogenous overproduction, although some patients are likely to experience both phenomena. (Choi et al, 2005b)

The mechanism underlying urate homeostasis was only recently reported by Enomoto (2002). Since urate exists primarily as a weak acid within the body, it was thought likely that the structure of any urate transporter would be similar to that of other organic anion transporters (OATs). Enomoto et al, 2002, identified a gene, and associated Deoxyribonucleic Acid (DNA), which they named URAT1, in the proximal epithelial cells of the human kidney, which they suggested as the mechanism by which extracellular urate is reabsorbed from the tubular lumen to the intracellular cytosol at the proximal tubules. (Enomoto et al, 2002) A range of other genetic associations with renal urate homeostasis have been described, (Anzai et al, 2012) but as they are not related to the main subject of interest, will not be considered further in this thesis.

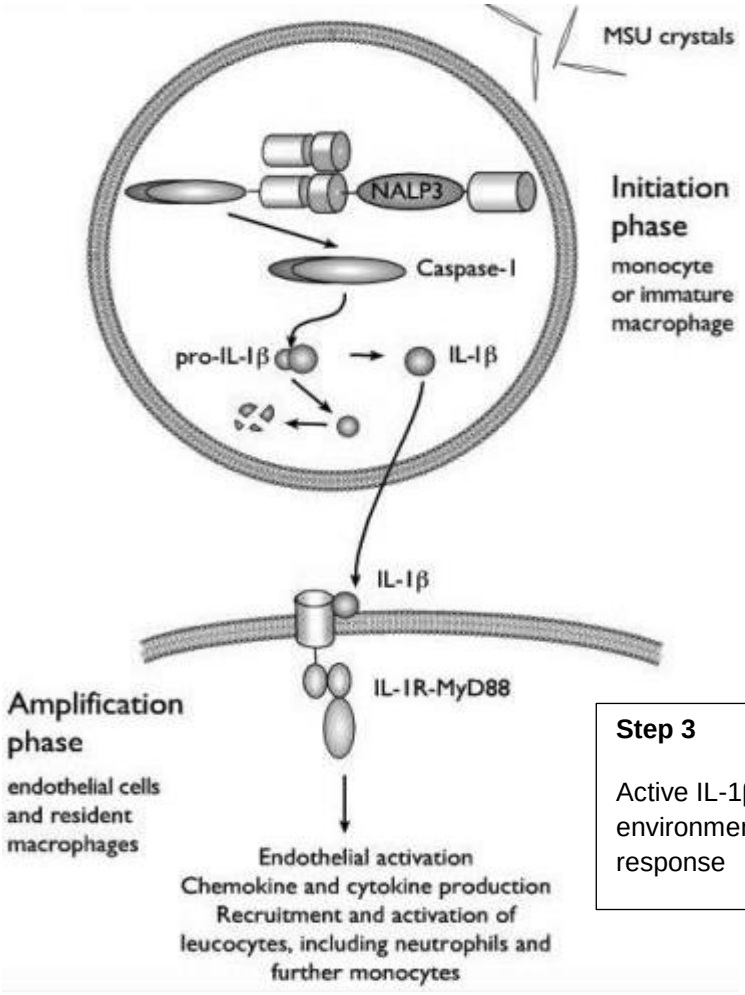
In most, this period of hyperuricaemia is asymptomatic, and whilst evidence suggests that higher levels of serum urate lead to an increased risk of MSU crystal deposition, even in patients with the highest levels of serum urate (>9mg/dL), only a minority of patients (22%) go on to develop gout. (Campion et al, 1987) However, in some, for reasons which are poorly understood, at a concentration of approximately 6.8mg/dL, when super-saturation of uric acid in the extracellular fluid is reached, precipitation and deposition of monosodium urate crystals in joints and soft tissues occurs. (Kippen et al, 1974; Loeb, 1972) How these sites of deposition are determined remains unclear.

Deposition of MSU crystals and cell-crystal contact results in intra-articular initiation of inflammation through a mechanism which remains unclear, but is thought to involve:

- phagocytosis of the synovial fibroblasts
- degranulation resulting in cell activation
- influx of leucocytes
- expression of pro-inflammatory and chemotactic molecules

Martinon et al, 2006, were the first to propose a stepwise underlying mechanism involving a multi-protein complex known as the “inflammasome” and resulting in increased production of the inflammatory cytokine Interleukin-1β (IL-1β). (Martinon et al, 2006) This mechanism is summarised in Figure 1.3 below.

Figure 1.3 Mechanisms underlying MSU crystal-induced inflammation



Step 1

MSU crystals stimulate intracellular danger signals detected by NOD-like receptors

Pro IL-1β released

Step 2

NALP and ASC proteins connect with and activate caspase-1 forming the "inflammasome"

The inflammasome mediates cleavage of Pro-IL-1β into active IL-1β

Step 3

Active IL-1β is released into the extracellular environment resulting in an acute inflammatory response

Adapted from (Dalbeth & Merriman, 2009)

Step 2 is considered the most relevant to crystal induced inflammation, since it is this step which involves activation of the "inflammasome", a multiprotein complex linking the identification of an intracellular danger signals by NOD-like receptors (NLR's), to the activation of pro-inflammatory cytokines.

Once activated, the inflammasome is formed by a member of the NACHT, LRR and pyrin domain-containing protein family (NALP 1, 2 or 3) and the adaptor protein ASC. The ASC protein connects the NALPs with, and activates a further protein Caspase-1, allowing cleavage of the pro-IL-1β into active IL-1β.

Martinon et al, 2006, reported this mechanism to be extremely sensitive with secretion of IL-1β after stimulation of monocytes by only very small amounts of MSU or calcium pyrophosphate dihydrate (CPPD) crystals and extremely specific since there was no secretion of IL-1β in response to presence of non-pathogenic crystals or particulate elements tested. Furthermore they reported that presence of a caspase-1 inhibitor was able to completely block MSU-induced IL-1β cleavage, confirming the role of caspase-1 in cleavage of the pro-IL-1β. (Martinon et al, 2006)

The resulting MSU crystal-induced inflammatory synovitis results in an acutely painful arthritis, most commonly of the first metatarsal joint, associated with swelling and overlying redness. These attacks are self-limiting, although the severe pain associated with acute attacks warrants prompt treatment. Studies have also identified evidence of subclinical inflammation persisting between acute attacks of gout, in the so called “intercritical” period. (Pascual et al, 1999; Roddy et al, 2013) This persistent inflammation implies a chronicity to the disease course of gout that was previously unrecognised by clinicians, and suggests that the disease remains active physiologically, even in the absence of clinical symptoms.

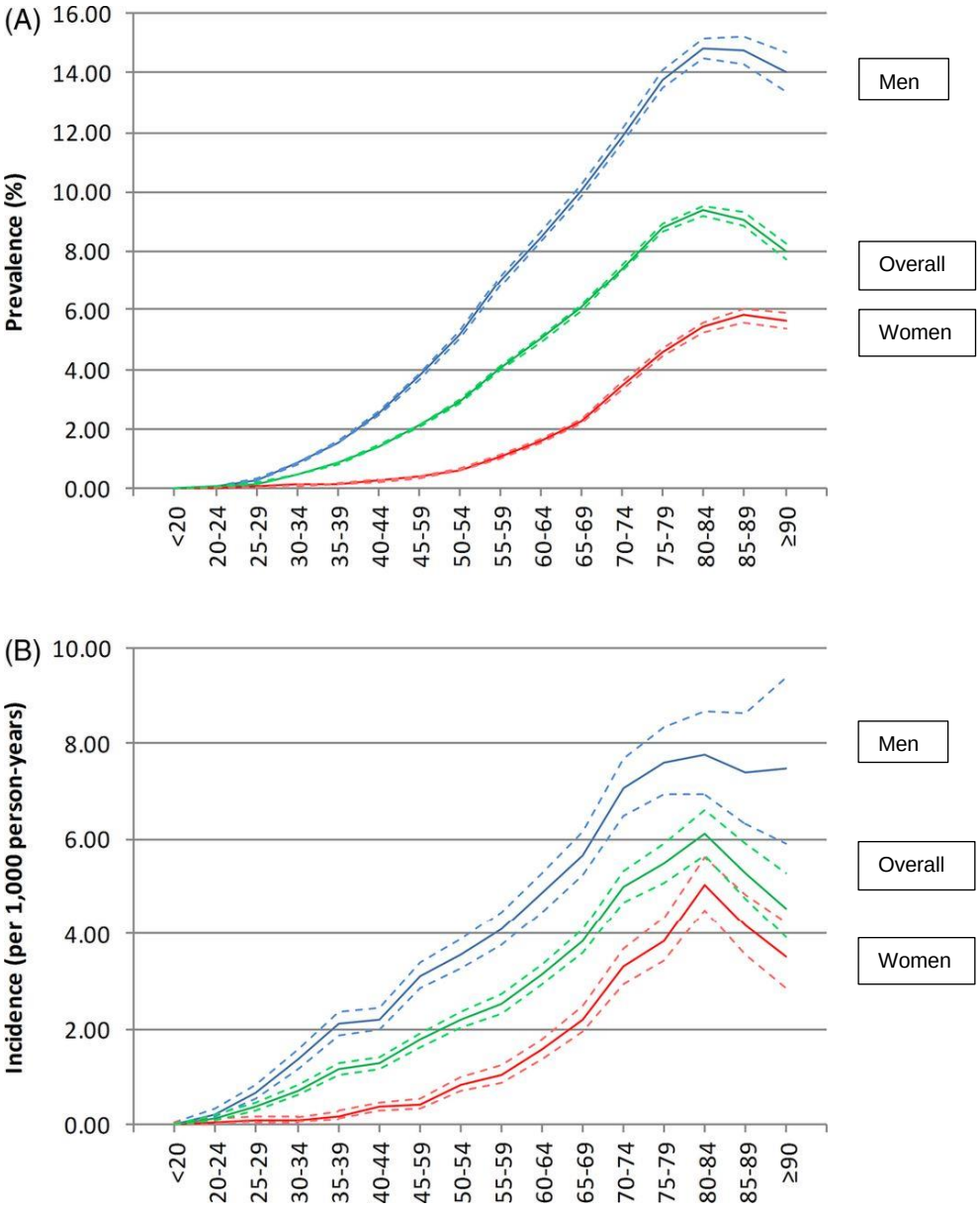
However, this raises an important question about why, in the ongoing presence of MSU crystals and sub-clinical inflammation, acute attacks are episodic suggesting additional factors influencing their onset. Similarly the reasons for, and mechanisms underlying, the self-limiting nature of acute attacks of gout are also likely to be multifactorial, but remain poorly understood.

1.4.1 The relationship between gout and age and gender

Increasing age and male gender are both recognised as risk factors for gout. (Choi et al, 2005b) This is demonstrated graphically in figure 1.4, taken from Kuo et al, 2014, describing the epidemiology of gout in the UK from 1990-1999. (Kuo et al, 2014)

Figure 1.4: Incidence & prevalence of gout in the UK by age and gender in 2012

Findings are shown by the solid lines with 95% confidence intervals by the dashed lines either side



Source: (Kuo et al, 2014)

The increased prevalence of gout in men was first described by Hippocrates:

> "A woman does not take the gout, unless her menses be stopped," (Adams, 1849)

This gender difference continues to be reported. (Choi et al, 2005b) Mechanisms for this include a higher baseline serum urate level, and higher prevalence of hyperuricaemia in men which may be caused by the uricosuric effect of oestrogen on the renal tubules leading to increased uric acid excretion in women. (Chen et al, 2012) This may also explain the increased incidence of gout in post-menopausal women. (Dirken-Heukensfeldt et al, 2010) Studies have shown that higher levels of uric acid increase the risk of gout in women, but that the strength of this association is considerably less among women than men, meaning that even with similar levels of blood urate, women have a lesser chance of developing gout than men. (Bhole et al, 2010) This is supported by findings of significantly higher blood urate concentrations in female gout patients, compared with male equivalents. (Puig et al, 1991) However, the physiological basis for these findings remain relatively poorly understood.

It is interesting to note that prevalence of gout in women peaks between ages 84-89 years, whereas in men it peaks between ages 80-84. This may be a manifestation of the healthy-survivor effect, since the life expectancy of men is shorter than that of women. It has been observed by other studies that mean age at onset of gout can be as much as 10 years older in women compared with men. (Chen et al, 2012) It has been suggest that this may be due to increased sensitivity of the kidneys to insulin in women, since insulin is known to reduce the

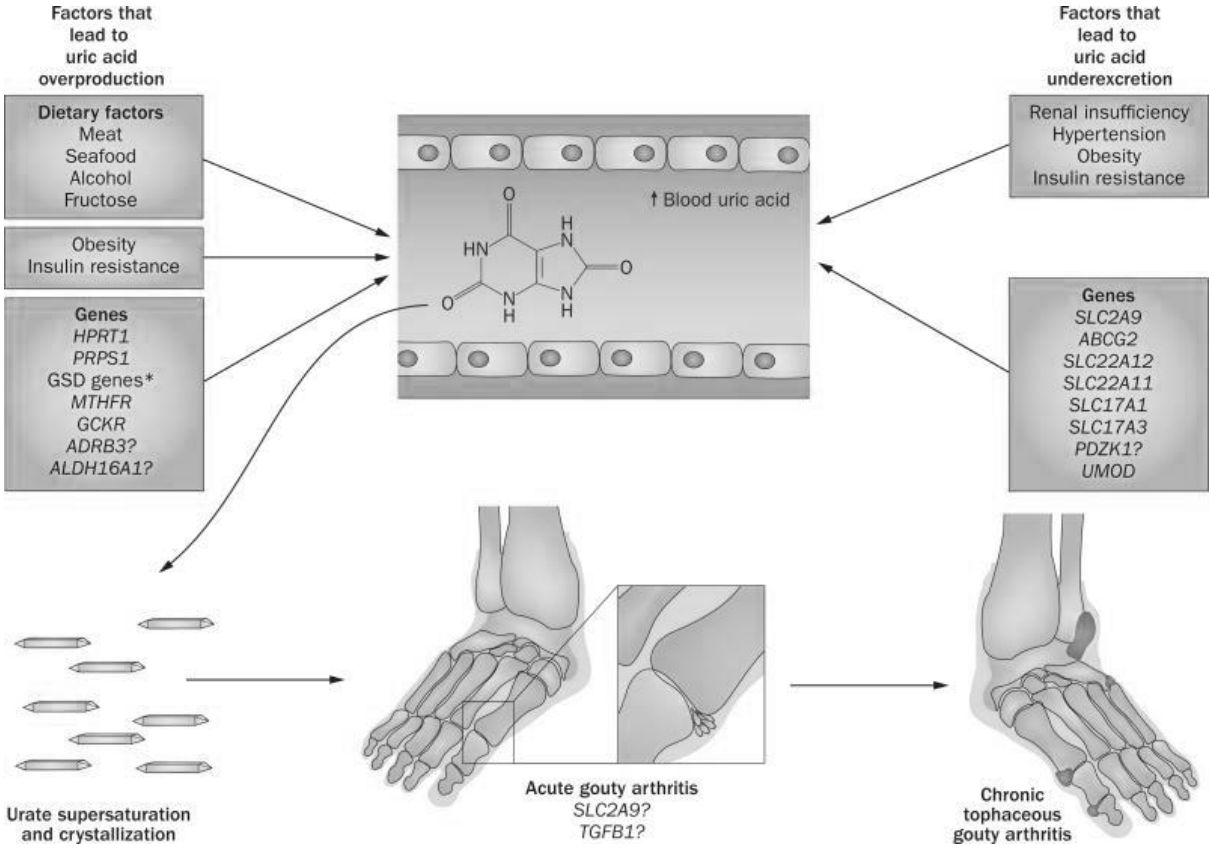
renal excretion of urate, and that higher prevalence of abdominal obesity with associated insulin-resistance, increased production and impaired excretion of uric in post-menopausal women may be a contributory factor. (Bhole et al, 2010)

However, to date, women remain a relatively understudied group in the epidemiology and clinical course of gout, and further research is required to gain understanding of the gender-specifics of gout.

1.4.2 The relationship between gout and genetic factors

Basal serum uric acid levels in humans are uniquely high, owing to three separate mutations resulting in a non-functioning uricase gene. (Riches et al, 2009) Hyperuricaemia is the strongest risk factor for incidence of gout, (Zhang et al, 2006b) and the heritability of hyperuricaemia has been shown in twin studies. (Emmerson et al, 1992; Krishnan et al, 2012) Links between common variants of several genes and hyperuricaemia have been demonstrated in recent studies, (Kolz et al, 2009; van der Harst et al, 2010; Yang et al, 2010) and these genes are thought to increase serum urate levels by contributing to either uric acid over production, or uric acid under-secretion. Known contributors to these mechanisms underlying hyperuricaemia are shown in Figure 1.5

Figure 1.5 Contributors to mechanisms underlying hyperuricaemia and gout



Source: (Reginato et al, 2012)

Most of the genes found to contribute to urate under-excretion encode transporter proteins found in the apical membrane of the human proximal renal tubule. (Reginato et al, 2012) These are summarised in Table 1.3.

Table 1.3a Variants at genetic loci SLC2A9 reported to associate with hyperuricaemia and gout

Location of mutation	Phenotype	Populations	References
SLC2A9 (chromosome 4) encoding glucose transporter type 9 (GLUT-9)			
Intron 3	SUA, FeUA, **gout**	European	Vitart et al, 2008
Intron 4	SUA, FeUA, **gout**	White African-American	Vitart et al, 2008;Doring et al, 2008; Wallace et al, 2008; Dehghan et al, 2008; Brandstatter et al, 2008 Charles et al, 2011; Tin et al, 2011
Exon 6	SUA, **gout**	White African-American Amish	Dehghan et al, 2008; Hollis-Moffatt et al, 2009;Karns et al, 2012 Tin et al, 2011 McArdle et al, 2008
Intron 6	SUA, **gout**	White Icelandic African-American	Doring et al, 2008; Kolz et al, 2009; Li et al, 2007; Stark et al, 2008; Karns et al, 2012 Sulem et al, 2011 Tin et al, 2011
Intron 7	SUA, FeUA, **gout**	European White African-American	Vitart et al, 2008; Karns et al, 2012 Doring et al, 2008; Li et al, 2007; Stark et al, 2008; Karns et al, 2012; Yang et al, 2010; Tin et al, 2011
Intron 8	SUA, **gout**	European	Tin et al, 2011
Intron 9	SUA, **gout**	African-American Croatian	Charles et al, 2011;Tin et al, 2011 Karns et al, 2012
Intergenic	SUA, **gout**	White Amish Croatian Pacific Islander New Zealand	Dehghan et al 2008 McArdle et al, 2008 Karns et al, 2012 Hollis-Moffatt et al, 2009 Hollis-Moffatt et al, 2009
Intergenic	SUA	Croatian African-American	Karns et al, 2012 Charles et al, 2011
Intergenic	**Gout**	Amish	McArdle et al, 2008

Table 1.3b Variants at genetic loci ABCG2 reported to associate with hyperuricaemia and gout

Location of mutation	Phenotype	Populations	References
ABCG2 (chromosome 4) encoding ATP-binding cassette subfamily G member 2 (ABCG2) an ATP dependent transporter protein			
Exon 2	SUA	Japanese	Matsuo et al, 2009
Exon 4	SUA, **gout**	Japanese	Matsuo et al, 2009
Exon 5	FeUA, SUA, **gout**	White African Chinese Icelandic Japanese Pacific Islander New Zealander	Kolz et al, 2009; Dehghan et al, 2008; Stark et al, 2008; Karns et al, 2012; Woodward et al, 2009 Dehghan et al, 2008; Tin et al, 2011 Wang et al, 2010 Sulem et al, 2011 Yamagishi et al, 2010; Matsuo et al, 2009 Phipps-Green et al, 2010 Caulfield et al, 2008; Phipps-Green et al, 2010
Intergenic	SUA	White	Kolz et al, 2009; Yang et al, 2010; Karns et al, 2012

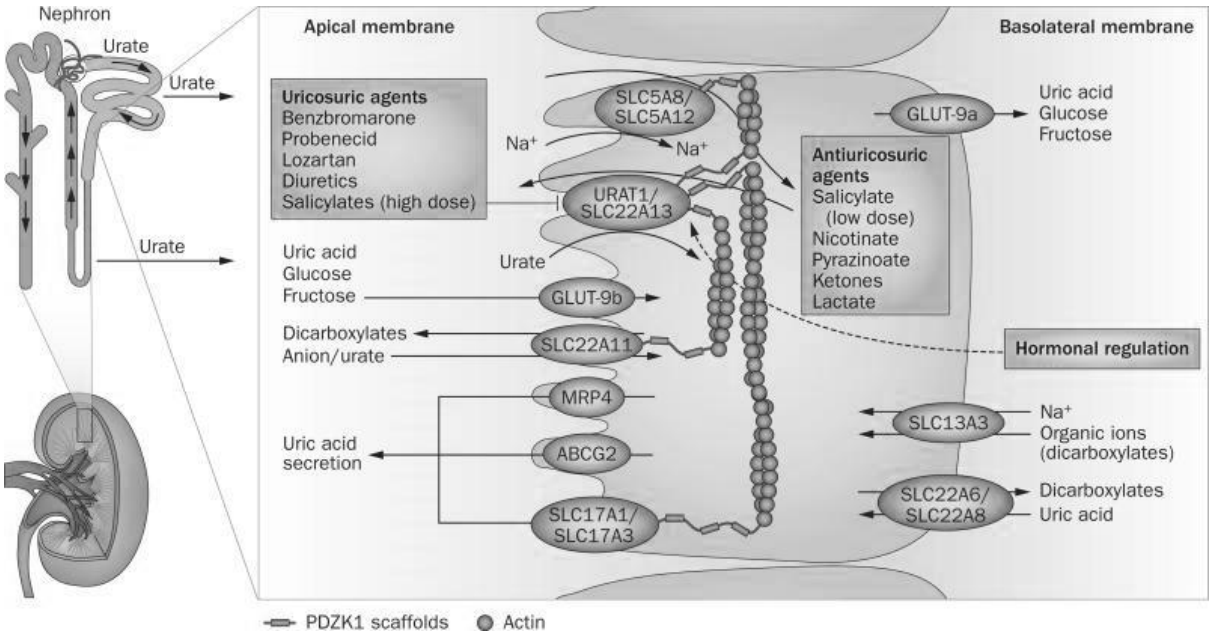
Table 1.3c Variants at genetic loci SLC22A12 reported to associate with hyperuricaemia and gout

Location of mutation	Phenotype	Populations	References
SLC22A12 (chromosome 11) encoding urate anion transporter 1 (URAT1)			
Exon 1	FeUA, SUA	Chinese White African-American	Tu et al, 2010 Kolz et al, 2009; Graessler et al, 2006 Tin et al, 2011
Exon 2	FeUA	German	Graessler et al, 2006
Exon 2	SUA	African-American	Tin et al, 2011
Intron 3	SUA	Chinese	Li et al, 2010
Intron 4	SUA	European Japanese Chinese	Kolz et al, 2009; van der Harst et al, 2010; Shima et al, 2006 Guan et al, 2009
Intron 4	FeUA, SUA	Korean	Jang et al, 2008
Intron 4	**Gout**	Chinese Solomon Islander	Tu et al, 2010 Tu et al, 2010
Exon 8	SUA, FeUA, **gout**	German Chinese Solomon Islander	Graessler et al, 2006 Tu et al, 2010; Li et al, 2010 Tu et al, 2010
Intergenic	SUA	European Africa-American	Kolz et al, 2009; Karns et al, 2012 Tin et al, 2011
Intergenic	FeUA, SUA	German Chinese	Graessler et al, 2006 Li et al, 2010
FeUA = Fractional excretion of uric acid, SUA = serum uric acid			

Adapted from Reginato et al, 2012 (Reginato et al, 2012)

These genetic loci have been identified to encode transporter proteins within the proximal renal tubule which influence renal urate excretion, and their actions are represented in Figure 1.6.

Figure 1.6 Contribution of known genetic variants to renal under excretion of urate



Source: (Reginato et al, 2012)

Twin and familial studies have shown a polygenic mode of inheritance for hyperuricaemia and renal excretion of urate, and the heritable component of hyperuricaemia has been estimated at between 40 and 60%. (Emmerson et al, 1992; Wilk et al, 2000) However, in contrast, relatively fewer of the loci identified influence the phenotypic expression of gout, with only 6% of variance in serum urate levels in patients with gout being explained by common genetic associations, and 67% being explained by non genetic factors. (Reginato et al, 2012) This would suggest that there are other important influences on the pathogenesis of gout beyond genetic predisposition to hyperuricaemia, in keeping with the evidence that only a minority of those with hyperuricaemia go on to develop clinical gout. (Choi et al, 2005b)

Single gene mutations predisposing to rare clinical syndromes associated with hyperuricaemia and gout, including Lesch-Nyhan Syndrome, (Ea et al, 2009) glycogen storage diseases, (Reginato & Olsen, 2007) and uromodulin defects, (Bleyer et al, 2003; Scolari et al, 2004) have also been identified. These monogenic mutations influence purine pathways, usually present at a young age and are often associated with additions non-gout clinical features. (Reginato et al, 2012) These are summarised in table 1.4 below.

Table 1.4: Rare Mendelian syndromes associated with hyperuricaemia and gout

Disease	Inheritance	Gene	Phenotype
Syndromes of altered purine metabolism			
HPRT related	XD	Hypoxanthine guanine phosphoribosyl transferase (HPRT 1)	Hyperuricaemia, gout, neurological dysfunction
PRPS related	XD	Phosphoribosyl pyrophosphate synthetase 1 (PRPS 1)	Hyperuricaemia, gout
Syndromes of excessive cell death and urate generation			
Glycogen storage disease type Ia	AR	Glucose 6 phosphatase	Growth retardation, hypoglycaemia, hepatomegaly, hyperuricaemia, gout, lactic acidosis
Glycogen storage disease type Ib	AR	Glucose six phosphate transporter	Growth retardation, hypoglycaemia, hepatomegaly, hyperuricaemia, gout, lactic acidosis
Glycogen storage disease type III	AR	Glycogen debranching enzyme	Early onset hyperuricaemia, gout
Glycogen storage disease type V	AR	Muscle glycogen phosphorylase	Early onset hyperuricaemia, gout
Glycogen storage disease type VII	AR	Muscle phosphofructokinase	Early onset hyperuricaemia, gout
Syndromes of reduced renal excretion of uric acid			
Medullary cystic kidney disease, type 1	AD	Unknown	Variable penetrance: renal dysfunction, hypertension, gout
Medullary cystic kidney disease, type 2	AD/AR	Uromodulin	Progressive renal dysfunction, variable hyperuricaemia, early onset gout
Familial juvenile hyperuricemic nephropathy	AD	Uromodulin	Progressive renal dysfunction, variable hyperuricaemia, early onset gout
AD= autosomal dominant; AR= autosomal recessive; XD=x-linked dominant; HPRT= Hypoxanthine guanine phosphoribosyl transferase; PRPS= Phosphoribosyl pyrophosphate synthetase			

Source: (Riches et al, 2009)

However, aside from these rare syndromes, the heritability of gout remains largely unproven. (Riches et al, 2009) Whilst mutations in genetic loci have been shown to play an important role in renal excretion of urate, thought to be a significant contributor to risk of gout, genetic factors have not yet been implicated in other mechanisms underlying gout pathogenesis, such as MSU-crystal formation and inflammatory response to MSU-crystals. (Merriman & Dalbeth, 2011) It may be that the genetic variations which influence these factors are yet to be identified, or that environmental factors are more important in the phenotypic expression of gout. (Krishnan et al, 2012) Comparison of clinical and genetic scoring systems to predict risk of gout also supports this latter suggestion, since whilst a scoring system based on differing combinations of genetic mutations thought to influence urate levels predicted a 41-fold increase in risk of gout compared to patients without such mutations, (Yang et al, 2010) a clinical score combining easily measureable risk factors including BMI, alcohol consumption, diuretic use and hypertension predicted an increased risk of gout of up to 79 times. (Choi et al, 2005a) It has therefore been suggested that the clinical utility of identification of genetic risk factors for gout is limited. (Reginato et al, 2012)

1.4.3 The relationship between gout and dietary factors

Diets that are rich in meat and alcohol have historically been blamed for the development of gout. The link between diet and gout was first observed by Hippocrates who dubbed it the “disease of kings”. (Adams, 1849) The influence of dietary components on hyperuricaemia has been reported by a number of studies, an unsurprising association given the mechanism by which urate is produced in

the human body is from the degradation of purines which derive mainly from the diet. (Choi et al, 2005; Choi et al, 2004a; Choi et al, 2007b; Choi & Curhan, 2008; Choi et al, 2009; Choi et al, 2010) As hyperuricaemia is the major risk factor for gout, it could reasonably expected that increased purine intake and resultant increased levels of uric acid should also increase likelihood of gout, however whilst consumption of some purine-rich foodstuffs, such as red meat and seafood, has been linked with an increased likelihood of gout, (Choi et al, 2004a) other dietary constituents such as purine-rich vegetables, which for the same reasons might reasonably be expected to increase the risk of gout, have not, although the reasons for this remain unclear. (Choi et al, 2004a) A summary of these relationships, adapted from the review by Dalbeth & So, 2010, is presented in table 1.5.

Table 1.5: Dietary constituents and risk of gout

Dietary constituent	Risk of incident gout	RR for risk of **gout*** (95%CI)	References
Foods			
Meat	Increased	1.41 (1.07-1.86)	(Choi et al, 2004a)[1]
Seafood	Increased	1.51 (1.17-1.95)	(Choi et al, 2004a)[1]
Purine-rich vegetables	No effect	0.96 (0.74-1.24)	(Choi et al, 2004a) [1]
High fat dairy products	No effect	1.0 (0.77-1.29)	(Choi et al, 2004a) [1]
Low fat dairy products	Reduced	0.58 (0.45-0.76)	(Choi et al, 2004a) [1]
Fructose rich fruits	Increased	1.64 (1.05-2.56)	(Choi & Curhan, 2008) [1]
Vitamin C	Reduced	0.55 (0.38-0.80)	(Choi et al, 2009) [1]

RR = Relative Risk; CI = Confidence interval

***** multivariate relative risk, typically comparing highest quintile of ingestion with referent group (no ingestion or lowest quintile of ingestion)

[1] Reports results from the Health Professionals Follow-up study which followed 47,150 men prospectively for up to 12 years

Dietary constituent	Risk of incident gout	RR for risk of **gout*** (95%CI)	References
Drinks			
Sugar sweetened soft drinks	Increased	M 1.85 (1.08-3.16) F 2.39 (1.34-4.26)	(Choi & Curhan, 2008) [1] (Choi et al, 2010) [2]
Diet soft drinks	No effect	M 1.12 (0.82-1.52) F 1.18 (0.87-1.58)	(Choi & Curhan, 2008) [1] (Choi et al, 2010) [2]
Fruit juice	Increased No effect	M 1.81 (1.12-2.93) F (orange juice) 2.42 (1.27-4.63) F (other juices) 1.14 (0.57-2.27)	(Choi & Curhan, 2008) [1] (Choi et al, 2010)[2]
Free fructose	Increased	M 2.02 (1.49-2.75) F 1.62 (1.20-2.19)	(Choi & Curhan, 2008) [1] (Choi et al, 2010)[2]
Coffee	Reduced	M 0.41 F 0.43	(Choi et al, 2007b) [1] (Choi & Curhan, 2010) [2]
Decaffeinated coffee	Reduced	M 0.73 F 0.77	(Choi et al, 2007b) [1] (Choi & Curhan, 2010) [2]
Tea	No effect	M 0.82 F 1.55	(Choi et al, 2007b) [1] (Choi & Curhan, 2010) [2]

RR= Relative risk; CI = Confidence interval

***** multivariate relative risk, typically comparing highest quintile of ingestion with referent group (no ingestion or lowest quintile of ingestion)

[1] Reports results from the Health Professionals Follow-up study which followed 47,150 men prospectively for up to 12 years

[2] Reports results from the Nurses' Health Study which prospectively followed 78,9.6 women for up to 22 years

Source: Adapted from Dalbeth & So, 2010 (Dalbeth & So, 2010)

The examination of the association between the incident phenotypic expression of gout, as opposed to asymptomatic hyperuricaemia, in the Health Professionals Follow-up Study has been not been reproduced. However, Zhang et al, 2012, have gone on to report an increased odds of recurrence of gouty attacks in those with existing gout in those with high consumption of plant based purines. (Zhang et al, 2012)

Current research has focused on investigating the interaction of genetic variants with dietary factors, since many of them encode anion transporters exchanging uric acid for the breakdown products of these dietary constituents. It has been suggested that the genetic mutations which predispose to gout exaggerate the hyperuricaemic response to other predisposing factors, and research is ongoing to establish interactions between particular genetic variants and dietary constituents which have been linked to increased risk of gout. (Dalbeth et al, 2014)

1.4.4 The relationship between gout and alcohol consumption

Alcohol intake, particularly port, has historically been linked with gout but it has shown that it was likely to be lead contaminants within port that were responsible for its precipitation of gout. (Ball, 1971) However existing literature supports the consumption of alcohol as a continuing risk factor in the development of gout. (Gibson et al, 1983; Sharpe, 1984) The Health Professionals follow up study demonstrated an association between alcohol and gout reporting differing levels of risk depending on the type of alcohol consumed, with beer conferring the greatest risk, and no increased risk reported between men who consumed 2 glasses of wine per day, compared to those who consumed one per month. (Choi et al, 2004b) Their findings are summarised in table 1.6 below.

Table 1.6: Summary of the association between alcohol consumption and risk of gout

Dietary factor	Risk of developing gout	RR for developing gout* (95%CI)	References
All alcohol	Increased	2.53 (1.73-3.70)	Choi et al, 2004 (b)[1] (Choi et al, 2004b)
Beer	Increased	2.51 (1.77-3.55)	Choi et al, 2004 (b)[1] (Choi et al, 2004b)
Spirits	Increased	1.60 (1.19-2.16)	Choi et al, 2004 (b)[1] (Choi et al, 2004b)
Wine	No effect	1.05 (0.64-1.72)	Choi et al, 2004 (b)[1] (Choi et al, 2004b)

RR = relative risk CI= confidence interval

* multivariate relative risk, typically comparing highest quintile of ingestion with referent group (no ingestion or lowest quintile of ingestion)

[1] Reports results from the Health Professionals Follow-up study which followed 47,150 men prospectively for up to 12 years

Adapted from: (Dalbeth & So, 2010)

This may be explained by the fact that beer contains purines in addition to alcohol. Standard beers have an alcohol content of about 1 gram per 100 mL, but also contain approximately 8 mg purines per 100 mL, with some, particularly low alcohol varieties containing more purines. (Gibson et al, 1983)

In addition to the direct intake of purines from beer, alcohol predisposes to gout through a mechanism of hyperuricaemia caused by accelerated synthesis of uric acid from adenosine, produced during alcohol metabolism, or via the reduced urinary excretion of uric acid due to the elevation of blood lactate produced by the oxidation of ethanol. (Nakamura et al, 2012) Lin et al, 2000, reported that excessive alcohol consumption, particularly binge drinking, was the most important factor in the development of gout, even when the serum urate level was less than 8mg/dL. (Lin et al, 2000) It is likely that this results from dehydration, and the relative increase in SUA levels resulting from a decrease in circulating volume.

1.4.5 The relationship between gout and diuretic use

Several drugs are known to increase serum uric acid levels with the strongest association being with diuretic drugs. Diuretics are thought to contribute to hyperuricaemia through renal mechanisms including reduced uric acid excretion, increased urate reabsorption and direct effects on urate transporters at the renal proximal tubule, (Hueskes et al., 2012) and the use of both loop and thiazide diuretics are thought to be one of the most common modifiable risk factors for gout. This is especially the case in the elderly and women, where the renal effects

of diuretics are likely to compound the effects of reduced post-menopausal oestrogen levels in further reducing renal urate excretion. (Doherty, 2009) A recent systematic review found that risk of gouty arthritis is increased in patients using diuretics, but noted only moderate quality of the included studies (n= 2 RCTs, 6 cohort and 5 case-control studies) and significant heterogeneity in study size, population and adjustment for potential confounders. (Hueskes et al., 2012) A major factor to be considered in this relationship is confounding by indication, since the indications for diuretics such as heart failure or hypertension, may be the true risk factors for developing gout.

1.5. Diagnosis of gout

Despite being the most common inflammatory arthropathy in the UK, there is evidence that gout is under-diagnosed. (Sturrock, 2000) This may relate to its natural disease course with two distinct modes of presentation, painful acute gout and “asymptomatic” chronic gout. Clearly, in the absence of the typical features of a gouty attack making a definitive clinical diagnosis is challenging.

Following the identification of MSU crystals in the synovial fluid of patients with gout by McCarthy and Hollander in the 1960’s, demonstrating the presence of these crystals within joints by aspiration of joint fluid for microscopic examination has become the “gold standard” for the diagnosis of gout. (McCarty & Hollander, 1961) Crystals can be identified during both the acute and chronic phases of the disease, from joints that are inflamed or not, and even joints previously unaffected by gouty attacks. (Pascual et al, 1999; Roddy et al, 2013) However, evidence suggests that this “gold standard” test is applied in only the minority of cases.

(Janssens et al, 2010a) Reasons for this are likely to be twofold: firstly joint aspiration is an invasive and painful procedure and patients, particularly those presenting with an acute flare, may be reluctant to undergo it. Secondly, is that the majority of gout patients are diagnosed and managed in primary care, (Pal et al, 2000; Rott & Agudelo, 2003; Zhang et al, 2006b) and primary care physicians may be less willing or skilled to undertake joint aspiration.

Thus, primary care physicians in particular have come to rely on clinical criteria for guidance in the diagnosis of gout. The first of these was proposed by Wallace et al, 1977, (summarised in Table 1.7) although not validated. (Wallace et al, 1977) Two recent publications have assessed the validity of the Wallace criteria in both primary, (Janssens et al, 2010b) and secondary care, (Malik et al, 2009) and found them lacking sensitivity and specificity.

The European League Against Rheumatism (EULAR) undertook a systematic literature review and expert consensus Delphi exercise in 2006 to establish 10 diagnostic statements to assist with the diagnosis of gout. Each statement was assessed for sensitivity, specificity and likelihood ratio (LR) of predicting diagnosis of gout. (Zhang et al, 2006b) In 2011, a group in the U.S.A. reviewed these recommendations, along with new evidence and issued 10 revised diagnostic recommendations. (Hamburger et al, 2011) The three sets of recommendations are presented side by side in table 1.7 below, to demonstrate their similarities in diagnostic clinical features and crystal identification. The differences relating to presence of hyperuricaemia, presence of MSU crystals in asymptomatic joints and screening for co-morbidities largely reflect the growth in understanding of the pathogenesis and epidemiology of gout since the Wallace criteria were published.

Table 1.7: Comparison between published diagnostic criteria for gout

Wallace, 1977 (Wallace et al, 1977)	**EULAR 2006** (Zhang et al, 2006b)	**Hamburger et al, 2011** (Hamburger et al, 2011)
Features suggestive of acute gout include • monoarthritis attack, • particularly a unilateral first MTP joint, or tarsal joint attack, • redness over the joint • maximal inflammation reached within one day	Features highly suggestive of acute crystal inflammation, though not specific for gout are: Rapid development of • severe pain, swelling, and tenderness • with overlying erythema • reaching its maximum within 6–12 hours	Features highly suggestive of acute crystal inflammation, though not specific for gout are: Rapid development of • acute monoarticular attacks of the lower limbs • severe pain, swelling, and tenderness, maximal within 6-12 hours • with overlying erythema
Diagnosis of gout also suggested by • Recurrent attacks of acute arthritis • Tophi	Clinical diagnosis reasonably accurate in typical presentations of gout, e.g. recurrent podagra with hyperuricaemia, but not definitive without crystal confirmation	Clinical diagnosis reasonably accurate in typical presentations of gout
MSU crystals in joint fluid aspirate: • Required for definitive diagnosis of gout • *During an acute attack*	Presence of MSU crystals in synovial fluid or tophus aspirates: • Required for definitive diagnosis of gout • Reliable even in the intercritical period	Presence of MSU crystals in synovial fluid or tophus aspirates: • Required for definitive diagnosis of gout • Reliable even in the intercritical period
Septic arthritis must be excluded • Joint fluid culture should be negative for organisms during an attack	Septic arthritis must be excluded using • Gram staining and culture of synovial fluid, even in presence of MSU crystals as gout and sepsis may coexist	Septic arthritis must be excluded using • Gram staining and culture of synovial fluid, even in presence of MSU crystals as gout and sepsis may coexist
Hyperuricaemia should be present	SUA levels neither confirm nor exclude gout • During an acute attack SUA levels may be normal	SUA levels neither confirm nor exclude gout • During an acute attack SUA levels may be normal
	Renal UA excretion should be determined in selected gout patients, especially • those with onset of gout <25 years or a family history of young onset gout • renal calculi	Assessment of renal UA excretion rarely necessary but should be considered in selected gout patients, • those with onset of gout <25 years or a family history of young onset gout • *lithogenic workup in those with renal stones*
X-ray findings suggestive of gout • Asymmetric swelling within a joint • Subcortical cysts without erosions	• X-rays may be useful in assessing chronic gout Not useful in diagnosis of early or acute gout	• X-rays may be useful in assessing chronic gout • Not useful in diagnosis of early or acute gout • Only necessary if a fracture is suspected
	Risk factors for gout *and associated co-morbidity* should be assessed, including • features of the metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, hypertension)	Risk factors for gout should be assessed, including • features of metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, and hypertension), CKD, medications, family history and lifestyle

Pelaez-Ballestas et al, 2010, undertook a cross-sectional study of MSU-crystal confirmed gout patients in Mexico, obtaining demographic and clinical features prospectively. (Pelaez-Ballestas et al, 2010) These clinical features were then compared to criteria recommended by Wallace et al, 1977 and Zhang et al, 2006 to determine what easily obtained clinical data might make a diagnosis of chronic gout highly likely, if joint aspiration were not possible. Janssens et al, 2010 using similar methodology, developed the Neijimegen scoring tool to determine which clinical features strongly predicted a diagnosis of acute gout. (Janssens et al, 2010a) The findings of these two studies are presented in Table 1.8 below for comparison.

Table 1.8**:** Comparison of clinical criteria for diagnosis of acute gout

Pelaez-Ballestas et al, 2010		Neijmegen Clinical Scoring Tool	
Criteria		Criteria	Clinical Score
Gout diagnosed by presence of ≥4/8 of:		Gout confirmed in over 80% with score of 8 or more:	
≥ 1 attack of acute arthritis		Male sex	2.0
Mono or oligoarthritis attacks		Previous patient-reported arthritis attack	2.0
Rapid pain and swelling (<24 hours)		Onset within 1 day	0.5
Erythema		Joint redness	1.0
Podagra Unilateral tarsiitis		MTP1 involvement	2.5
Possible tophi		Hypertension or ≥1 cardiovascular diseases [a]	1.5
Hyperuricaemia		Serum uric acid level >5.88mg/dL	3.5
Maximum Score	8.0	Maximum Score	13.0
		MTP1= first metatarsophalangeal joint; [a] angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease	

Source: (Janssens et al, 2010a); (Pelaez-Ballestas et al, 2010)

1.6 Clinical features of gout

1.6.1 Acute gout

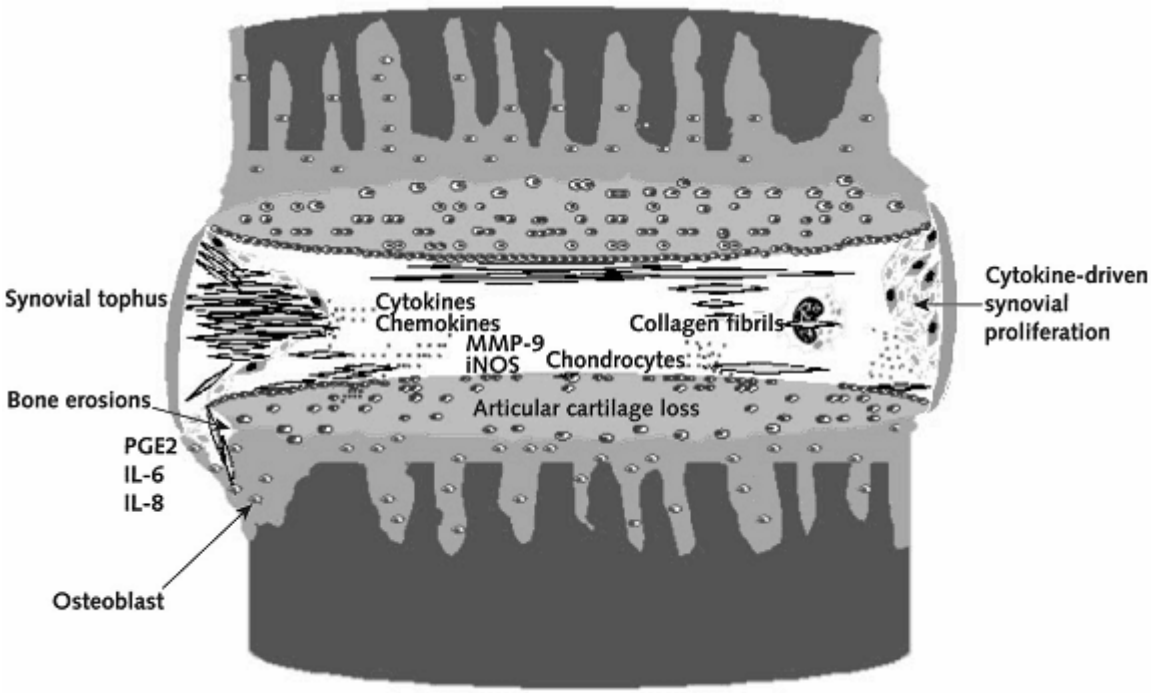
Acute attacks of gout present with a rapid onset of symptoms resulting from synovitis triggered by MSU crystal deposition within joints. These attacks have a characteristic presentation in that they are excruciatingly painful, with maximal pain and inflammation often reached within 12 hours, and are self-limiting, lasting on average between 7 and 10 days. Recurrence is common, with approximately two thirds of patients with at least one gout attack in the previous year experiencing a recurrent attack. (Neogi et al, 2006)

The first acute attack affects the first MTP joint in 56-78% of patients, with 90% having acute gout of the great toe at some point in their disease course. (Roddy, 2011) Several theories exist as to the reason for acute attacks of gout favouring the first MTP joint. These include cooler temperature of peripheral joints, susceptibility of the foot to trauma which contributes to crystal formation, and a preference for crystal deposition at joints also affected by osteoarthritis (OA), common in the first MTP joint as a result of the aforementioned factors combined with extraordinary biomechanical stress on that particular joint. (Roddy, 2011) Other commonly affected joints include joints of the foot, ankle, knee, wrist, finger and elbow but mechanisms behind this joint distribution are unclear.

1.6.2 Chronic gout

Chronic uncontrolled hyperuricaemia can lead to tophi, which result from deposition of urate crystals in the soft tissues, tendon sheaths, and bony prominences. These tophi can cause joint deformity and destruction, but can also cause localised pressure effects, and form the site for inflammation, ulceration and infection. (Kumar & Gow, 2002) Within the joint itself, chronic hyperuricaemia and gout may lead to joint damage and the typical "punched out" erosions seen (represented in Figure 1.7).

Figure 1.7: The effect of chronic gout on synovial joints



Source: (Choi et al, 2005b)

Tophi are thought to develop within 5 years of the onset of gout in 30% of untreated patients, (Schumacher et al, 2005) with this figure rising to 75% of patients with untreated gout for 20 years or more. (Gutman, 1973) Many years of

sustained normouricaemia are required before tophi can be seen to recede. (Kumar & Gow, 2002)

Chronic gout also predisposes to co-morbidities such as hypertension, diabetes and renal disease, and these associations will be discussed in more detail in Chapter 2.

1.7 Management of gout

The majority of patients with gout are diagnosed and managed in primary care, with less than 10% being referred to a rheumatologist. (Pal et al, 2000) Having discussed diagnostic tools for use in primary care, this section will briefly discuss the primary care management of both acute and chronic gout.

Effective treatments are available for both acute and chronic gout, with evidence to suggest that with optimal drug management gout can be considered a curable disease. (Li-Yu et al, 2001)

1.7.1 Management of acute gout

Since patients presenting with acute gout are experiencing severe pain, treatments must be targeted at rapidly reducing inflammation and pain. Several options exist including non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase II (COX II) inhibitors, colchicine, and oral or parenteral corticosteroids. UK national guidance from the British Society of Rheumatology (BSR), (Jordan et al, 2007) European guidance from the European League Against Rheumatism (EULAR), (Zhang et al, 2006a) and US guidance from the American College of

Rheumatology (ACR), (Khanna et al, 2012b) on the management of acute gout are summarised in Table 1.9. The BSR and EULAR guidance are very similar in recommending monotherapy with NSAIDs as a first line treatment for all acute gout (in the absence of contraindications). The ACR guidelines take much more of an individual approach, recommending that treatment decisions should be based upon the severity of pain and number of joints affected, endorsing combination therapy as a first line for severe or polyarticular attacks, and endorsing use of newer interleukin (IL)-receptor antagonists that are not yet part of the BSR or EULAR recommendations.

Table 1.9: Comparison of the BSR, EULAR and ACR guidelines for the management of acute gout.

	BSR (Jordan et al, 2007)	EULAR (Zhang et al, 2006a)	ACR (Khanna et al, 2012b)
General advice	• Rest affected joints • Start treatment with an anti-inflammatory drug immediately and continue for 1-2 weeks	None given	• Treatment should be initiated with 24 hours of onset • Severity should be assessed and inform choice of therapy
Medication of choice	• Fast acting oral NSAIDs at maximum doses if there are no contraindications	• NSAID if no contraindications	• Mild/moderate pain (≤6 on VAS) or 1-3 small or 1-2 large joints affected monotherapy with any of NSAID, colchicine (1.8g over first hour then 0.6mg bd-tds) or systemic corticosteroids (prednisolone 0.5mg/kg/day for 5-10 days) • Severe pain/polyarticular use combination therapy • NSAID + colchicine • Colchicine + oral steroid • NSAID + colchicine + IA steroid
	• Colchicine 0.5mg bd – qds as an alternative • Slower to work than NSAIDs	• Colchicine (at low dose e.g. 0.5mg bd-tds to avoid side effects) as an alternative	
Gastroprotection	• Co-prescription of gastro-protective agents should follow standard guidelines for the use of NSAIDs and Coxibs	Not stated	• Do not combine oral corticosteroid and NSAID due to risk of serious GI side effects
Allopurinol in acute attacks	• Allopurinol should not be commenced during an acute attack • Continue established allopurinol and treat the acute attack conventionally	Not stated	• Can be initiated during an attack provided appropriate anti-inflammatory medication has already be initiated • Continue urate lowering therapy during an acute attack
Adjunctive medication	• Opiate analgesics can be used as adjuncts	• Intra-articular aspiration and injection of a long acting steroid can be used as an adjunct	• Inadequate response to mono-therapy - use or add an appropriate alternative agent
	• Intra-articular, oral, IM or IV corticosteroids can be used as an adjunct		• Inadequate response to combination therapy - use anakinra 100mg s/c daily or canakinumab 150mg s/c daily for 3 days
	• Diuretics used to treat • hypertension should be stopped • heart failure should be continued	• If gout associated with diuretic therapy, stop the diuretic if possible.	

1.7.2 Management of chronic gout

The primary goal in the management of chronic gout is suppression of serum urate. Li-Yu et al, 2001, demonstrated that maintenance of a serum urate level of <6mg/dL reduced acute gout flares. (Li-Yu et al, 2001) To this end urate lowering therapy (ULT) is paramount in preventing long term sequelae and recurrent attacks. The most frequently used ULT is allopurinol (a xanthine oxidase inhibitor), as although an alternative xanthine oxidase inhibitor, febuxostat, is available usage is limited by its high cost relative to allopurinol. UK national guidance from the BSR, (Jordan et al, 2007) European guidance from EULAR, (Zhang et al, 2006b) and US guidance from the ACR, (Khanna et al, 2012b) on the management of chronic gout are presented in Table 1.10 below. Both the BSR and EULAR guidelines emphasise the key role of allopurinol as first line treatment, with other uricosurics such as sulphinpyrazone or benzbromarone, used as second line agents in those unable to tolerate them. However, whilst the ACR guidelines recommend xanthine oxidase (XO) inhibitors as first line ULT, they do not specify whether allopurinol or febuxostat should be used preferentially. The ACR also endorse initiation of ULT during an acute attack provided that appropriate anti-inflammatory treatment has been started, whilst the BSR and EULAR guidance explicitly advise against this.

Table 1.10**:** Comparison of the BSR,EULAR and ACR guidelines on the management of chronic gout

	BSR (Jordan et al, 2007)	EULAR (Zhang et al, 2006b)	ACR (Khanna et al, 2012b)
Criteria for initiation of ULT	A second or further attacks within 1 year OR Presence of any of • tophi • renal insufficiency • uric acid stones • ongoing treatment with diuretics	• Recurrent acute attack • Arthropathy • Tophi • Radiographic changes of gout	• ≥2 acute attacks per year • Tophi • CKD Stage 2 or worse • Past urolithiasis
Timing of initiation	No sooner than 1-2 weeks after resolution of acute attack	Not stated	Can be started during acute attack provided anti-inflammatory medication already initiated
Choice of ULT	Allopurinol (dose adjusted for renal function)	Allopurinol (dose adjusted in renal impairment)	XO inhibitor - either allopurinol (dose adjusted in renal impairment) or febuxostat
Co-prescription of prophylaxis	• Colchicine 0.5mg bd, continued for up to 6 months or • NSAID or coxib for no more than 6 weeks	• Colchicine (0.5-1mg daily) and/or • NSAID (with gastro-protection if indicated)	• Colchicine (0.6-1.2mg daily) or • NSAID (with gastro-protection if indicated) • Prednisolone ≤10mg OD if NSAID and colchicine not tolerated • Continued for greater of 6 months or 3 months after achieving SUA target if no tophi present/ 6 months if tophi present
Titration	• Start at 50-100mg per day • Increase by 50-100mg every few weeks if required	• Start at low dose (100mg OD) • Increase by 100mg every 2-4 weeks if required	• Start at ≤100mg OD (50mg in CKD Stage 4 or above) • Titrate every 2-5 weeks
Target urate level	< 300micromol/l	≤360 micromol/L (6mg/dL)	Individual to each patient : **minimum target** ≤360 micromol/L (6mg/dL) but lower target may be required
Duration of treatment	Not stated	Not stated	Indefinite
Second choice of medication	Uricosuric agents can be used second line in • Patients who under-excrete uric acid • Resistance to, or intolerance of allopurinol • Sulphinpyrazone (200-800mg/day) preferred where renal function normal • Benzbromarone (50-200mg/day) if mild/moderate renal insufficiency	If allopurinol toxicity occurs consider • Other xanthine oxidase inhibitor (febuxostat) • Uricosuric agent if normal renal function (benzbromarone in renal insufficiency but hepatotoxicity risk) • Allopurinol desensitisation (only in cases of mild rash)	Uricosurics if intolerant or resistant to one XO inhibitor • Probenecid preferred in those with normal renal function • Measurement of urinary uric acid should precede initiation of uricosurics

Newer targeted therapies are becoming available. Immunomodulatory therapies with interleukin receptor antagonists such as anakinra, canakinumab and rilonacept, have been developed to combat the release of IL-1β on stimulation of the NALP3 inflammasome by MSU crystals. (So et al, 2009; So et al, 2007; Terkeltaub et al, 2009)

Since the absence of the uricase enzyme in humans was discovered, synthetic uricase has been suggested as a potential therapy for hyperuricaemia and gout. Rasburicase was the first of these, showing promising reduction in SUA and size of tophi, but adverse reactions were experienced by 80% of experimental subjects. (Richette et al, 2007) Pegloticase is a porcine-like recombinant uricase, but despite significant reductions in SUA and size of tophi, it was also associated with high incidence of serious adverse reactions, and as such is not in common usage at present. (Sherman et al, 2008)

1.7.3. Guidelines for holistic management of gout patients

Both UK national guidance from the BSR, (Jordan et al, 2007) European guidance from EULAR, (Zhang et al, 2006b) and US guidance from the ACR, (Khanna et al, 2012a) emphasise that advice on dietary and lifestyle modification should always be offered to all patients with gout as an adjunct to whatever form of pharmacological treatment they receive, and that a holistic view of the management of gout should be considered. These recommendations are summarised in table 1.11 below.

Table 1.11: Comparison of the BSR, EULAR and ACR advice on the holistic management of gout

BSR (Jordan et al, 2007)	EULAR (Zhang et al, 2006b)	ACR (Khanna et al, 2012a)
Lifestyle factors		
• Optimise weight • Increase exercise • Modify diet • Reduce alcohol intake • Maintain fluid intake	• Weight loss if obese • Modify diet • Reduce alcohol intake	• Weight loss if obese • Modify diet • Limit alcohol intake
Co-morbidity		

Treat underlying cardiovascular risk
 	
The effect of aspirin on SUA is bimodal:
• Aspirin in analgesic doses (600-2400 mg/day should be avoided
• Aspirin for cardiovascular prophylaxis (75-150mg) should be used appropriately
	• Associated comorbidity and risk factors should be addressed, such as
	  ○ Hyperlipidaemia
	  ○ Hypertension
	  ○ Hyperglycaemia
	  ○ Obesity
	  ○ Smoking
	• For hypertension consider losartan
	• For hyperlipidaemia consider fenofibrate
	• Both have modest uricosuric effects
		• Address comorbidity checklist
		  ○ Metabolic syndrome
		  ○ Type 2 Diabetes
		  ○ Hypertension
		  ○ Hyperlipidaemia/other modifiable risk factors for cardio or cerebrovascular disease
		  ○ History of urolithiasis
		  ○ CKD, glomerular or interstitial renal disease
		• Consider PCR testing for HLA-B*5801 in selected patients at high risk of severe allopurinol sensitivity reactions (Koreans with Stage 3 CKD or worse; Han Chinese and Thai irrespective of renal function)
		• Eliminate non-essential drugs which may contribute to hyperuricaemia
		• Consider use of losartan and fenofibrate as part of ULT

From table 1.11, it is clear that these general recommendations are very similar, and reflect the reduction, or management of, some of the major modifiable risk factors for gout, and common co-morbidities associated with gout. The ACR guidelines suggest testing for genetic variants that may predispose to a serious adverse reaction to allopurinol in patients of particular ethnicities, which the BSR and EULAR guidelines do not, but this may reflect wider access to this relatively costly test, a greater proportion of the ethnicities at risk within the US population, or simply that this test was not available when the BSR and EULAR guidelines were written.

1.8 Impact of Gout

Chronic gout impacts on long-term health in a number of ways. This is supported by a systematic review which concludes that gout is associated with reduced health-related quality of life, particularly in the physical function domains. (Chandratre et al, 2013)

There have been no recent studies of the economic burden of gout in the UK, although in 2007 approximately 26,119 in-patient bed days were attributable to gout, and in 2008 3.3 million prescriptions for allopurinol were issued at a cost of over £4.2 million. (Parsons et al, 2011)

Studies in the USA have reported that the annual cost to employers for employees with gout is nearly twice that of those without gout, with higher costs for medical claims, prescription claims, sick leave, short-term disability and workers compensation benefits. (Brook et al, 2006) Workers with gout were likely to have 5 more sick days than those without gout, which translates to an annual loss of in the region of 2.6 billion dollars. (Wertheimer et al, 2013) It is estimated that gout-

related health care costs are in the region of 4 billion dollars, resulting in an estimated total cost of gout to the US economy of in excess of 6 million dollars. (Wertheimer et al, 2013)

Smith et al, 2014, examined the global burden of gout and placed it 138th out of 291 conditions ranked in terms of years lived with disability, and that this has significantly increased over the last 10 years, and ranked gout 173rd of 291 in terms of overall disability burden. (Smith et al, 2014)

1.9 Summary

This section has introduced gout, the condition of interest for discussion in this thesis, and the important epidemiological, pathophysiological and clinical features of this condition.

Chapter 2: The relationship between inflammatory and vascular disease

2.1 Overview

This chapter will discuss existing evidence examining associations between inflammatory conditions and subsequent vascular disease, and the mechanisms which underlie these relationships. The evidence examining an association between gout and vascular disease will then be discussed as it relates to the aims and objectives of this thesis.

2.2 Background

Inflammatory disorders may affect a number of body systems including the skin, respiratory, gastrointestinal, and rheumatological systems. Clinical manifestations may differ but the mechanism underlying these diseases is similar and results from the triggering of inflammatory pathways and the subsequent release of pro-inflammatory cytokines. A number of inflammatory conditions, both rheumatological and otherwise, have already been linked with increased risk of vascular disease, suggesting that as a chronic inflammatory disease, gout may also confer such an additional risk.

2.3. Inflammatory conditions associated with vascular disease

Current evidence examining the relationship between inflammatory rheumatological conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and polymyalgia rheumatic (PMR), and non rheumatological

inflammatory conditions such as psoriasis and inflammatory bowel disease is discussed in this section.

2.3.1 Inflammatory rheumatological conditions and risk of vascular disease

2.3.1.1 Prevalence of vascular diseases

An increased prevalence of vascular diseases has been reported in patients with RA, ankylosing spondylitis (AS), and SLE. (Roman et al, 2003; Szabo et al, 2011; Wolfe et al, 2003) RA has been reported to be associated with a 30-60% increase in prevalence of cardiovascular disease, (Naranjo et al, 2008; Wolfe et al, 2003) although studies reporting prevalence of cerebrovascular disease in RA are conflicting. (Naranjo et al, 2008) AS has been associated with a 30% increase in prevalence of ischaemic heart diseases (IHD) and a 25% increase in prevalence of cerebrovascular disease, (Szabo et al, 2011) whilst SLE, in addition to cardiovascular and cerebrovascular risks has also been associated with an increased prevalence of peripheral vascular disease. (June & Scalzi, 2013)

2.3.1.2 Incidence of vascular diseases

Recent meta-analyses confirmed an increased incidence of vascular disease in patients with rheumatoid arthritis, (Avina-Zubieta et al, 2012; Zoller et al, 2012) of a similar magnitude to that found in patients with diabetes. (Peters et al, 2009) A meta-analysis of observational studies examining the association between rheumatoid arthritis and incident vascular disease reported risk of incident stroke to be increased by 40%, incident CVD to be increased by almost 50%, risk of

incident MI by almost 70%, and risk of incident heart failure by almost 90%. (Avina-Zubieta et al, 2012) A further meta-analysis also reported a 60% increase in incidence of ischaemic stroke and more than double the risk of incident haemorrhagic stroke. (Zoller et al, 2012)

Several cohort studies report on incidence of vascular diseases associated with SLE. (Hak et al, 2009; Magder & Petri, 2012; Zoller et al, 2012) A recent systematic review summarised the findings from relevant observational studies examining incident vascular disease in patients with SLE, reporting a two-three fold increase in incident cardiovascular disease, a 2-10 fold increase in incident MI, and a 2-8 fold increase in incident cerebrovascular disease. (Schoenfeld et al., 2013) The incidence of vascular disease in patients with spondyloarthropathies has been reported by a number of recent cohort studies, but this data is yet to be meta-analysed. (Bremander et al, 2011; Huang et al, 2013; Keller et al, 2014; Zoller et al, 2012) A one-and-a-half-fold increased risk of incident IHD was reported in patients with ankylosing spondylitis, (Huang et al, 2013) and a doubling of risk of morbidity from IHD also reported. (Bremander et al, 2011) A two-fold increased incidence of cerebrovascular disease is reported elsewhere, (Keller et al, 2014) with a further study suggesting that this overall risk is predominantly due to an increased risk of haemorrhagic stroke (SIR 2.72 (1.96-3.67)) compared to ischaemic stroke (SIR 1.23 (1.01-1.48)). (Zoller et al, 2012)

A recent systematic review reported PMR to be associated with an increased incidence of cerebrovascular events, MI and PVD, (Hancock et al, 2012) with a subsequent study demonstrating ischaemic and haemorrhagic stroke to be increased by a similar 50% in patients with PMR. (Zoller et al, 2012) The same

study reports an increase incidence of haemorrhagic stroke but not ischaemic stroke in patients with systemic sclerosis. (Zoller et al, 2012)

2.3.1.3 Mortality from vascular diseases

Rheumatoid arthritis has been shown to increase risk of mortality from vascular causes in a recent meta-analysis of observational studies. (Aviña-Zubieta et al, 2008) This study reported a 50% increase in mortality from CVD, a 60% increase in mortality from IHD, and a 60% increase in mortality from stroke in patients with rheumatoid arthritis compared to those without. (Aviña-Zubieta et al, 2008)

Three meta-analyses report on mortality from vascular disease associated with SLE. Pooled risk of all vascular mortality was reported to be approximately two and a half times that of those without SLE (SMR 2.59 (1.95-3.44)). (Toledano et al, 2012) They reported the risk to be highest in women (SMR 2.50 (2.31-2.70)) compared to men (SMR 1.90 (1.64-2.20)). (Toledano et al, 2012) Two further meta-analyses reported a similar two to four-fold risk of mortality from cardiovascular causes. (Schoenfeld et al., 2013; Yurkovich et al, 2014) However, the greatest risk was found in patients diagnosed at a younger age, with those aged 20-39 at the time of diagnosis at sixteen times the risk of death from cardiovascular cause compared to controls. (Schoenfeld et al., 2013)

Spondyloarthropathies have also been linked with increased risk of cardiovascular mortality. Two retrospective cohort studies report a 60-80% increased cardiovascular mortality associated with AS, (Bakland et al, 2011; Mok et al, 2011) whilst a recent meta-analysis reported a 36% increase in risk of

cardiovascular mortality associated with psoriatic arthropathy. (Toledano et al, 2012)

A recent meta-analysis has also reported a 3-fold increase in cardiovascular mortality associated with systemic sclerosis and 5 fold-increase in cardiovascular mortality associated with vasculitis, (Toledano et al, 2012) and a systematic review reported an association between PMR and increased risk of vascular mortality, although there was significant heterogeneity between studies which precluded formal meta-analysis. (Hancock et al, 2012)

2.3.2 Other inflammatory conditions and risk of vascular disease

2.3.2.1 Incidence of vascular diseases

Two recent meta-analyses of cohort studies reported an increased incidence of vascular diseases in patients with the inflammatory skin condition psoriasis. (Horreau et al, 2013; Miller et al, 2013) In the first, mild psoriasis was associated with a 20% increased risk of any vascular event, including cardiovascular and cerebrovascular events, and this excess risk increased to 60% in patients with severe psoriasis. (Horreau et al, 2013) They also reported a 25% increased incidence of MI, 20% increased incidence of coronary artery disease, but no increased incidence of cerebrovascular disease associated with psoriasis. The same systematic review identified four studies which examined risk of incident peripheral vascular disease associated with psoriasis. (Horreau et al, 2013) Three of the four reported this risk to be increased by between 25% and 98%, with the highest increase in risk estimated by the only one of the three studies to adjust for

potential confounders. (Prodanovich et al, 2009) The second meta-analysis reported similar associations with incident vascular disease of an increased magnitude. (Miller et al, 2013) Psoriasis was associated with a 40% increased risk of any incident cardiovascular disease and a 50% increase in incident ischaemic heart disease. A 50% increased risk of incident PVD, and no increased risk of cerebrovascular disease associated with psoriasis was also reported, similar to that found by Horreau et al, 2013. (Horreau et al, 2013; Miller et al, 2013)

Dermatomyositis, an inflammatory skin and muscle condition, has also been linked with increased risk of incident vascular diseases. The risk of MI in patients with this condition has been reported to be three-times that of those without the condition, and risk of ischaemic stroke reported to be increased to by two-thirds. (Lai et al, 2013)

The inflammatory bowel diseases ulcerative colitis (UC) and Crohn's disease are both associated with increased incidence both ischaemic and haemorrhagic stroke. (Zoller et al, 2012) Excess risk of ischaemic stroke was similar (between 20% and 30%), but risk of haemorrhagic stroke was higher in Crohn's disease (80%) than in UC (37%). (Zoller et al, 2012) A similar trend was also seen in risk of stroke associated with sarcoidosis, where excess risk of ischaemic stroke was reported to be approximately 20% and risk of haemorrhagic stroke higher at 60%. (Zoller et al, 2012)

2.3.2.2 Mortality from vascular diseases

Studies examining the relationship between inflammatory bowel disease and vascular mortality report conflicting results. One meta-analysis reported excess

mortality from all vascular causes to be 50% higher in patients with Crohn's compared to those without, (Toledano et al, 2012) and yet two others found no statistically significant relationship between either Crohn's disease or UC and cardiovascular mortality. (Bewtra et al, 2013; Dorn & Sandler, 2007)

No statistically significant risk of cardiovascular mortality has been reported in association with psoriasis. (Miller et al, 2013)

No studies were identified which reported mortality in inflammatory muscle conditions.

2.4 Mechanisms underlying the association between inflammatory disorders and vascular disease

This section will discuss vascular disease, including the anatomical sites at which it is commonly found, the clinical presentations and pathogenesis responsible, and the mechanisms by which inflammatory conditions are thought to predispose to it.

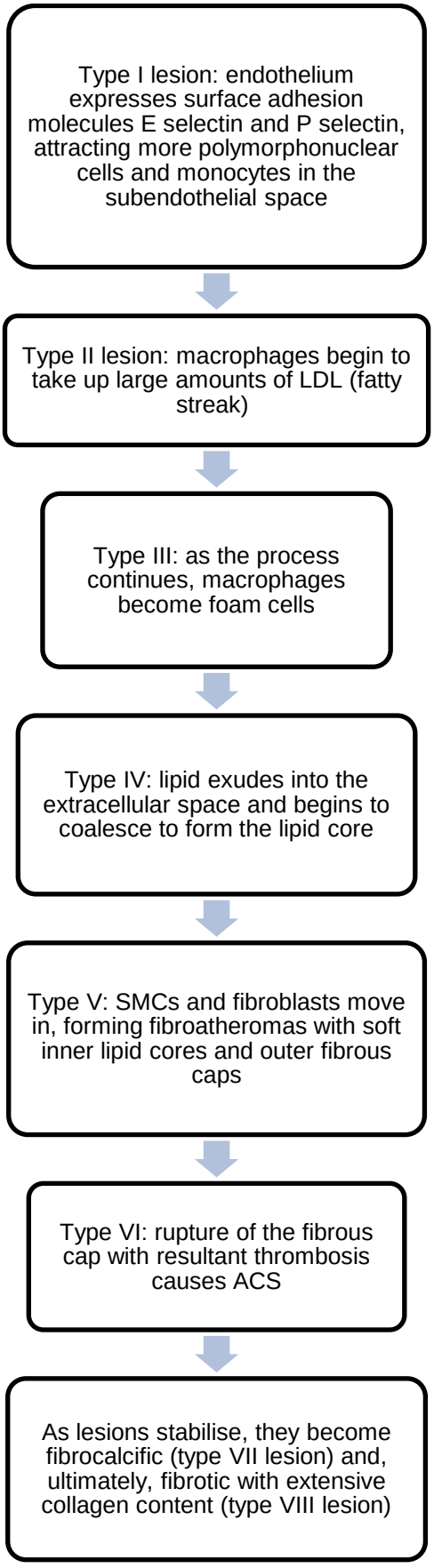
2.4.1 Pathogenesis of vascular disease

The onset of vascular disease is triggered by damage to arterial walls resulting from stressors such as hypertension, which results in impaired arterial elasticity and narrowing of the vessel lumen by atherosclerotic plaques. Plaque deposition predisposes to vascular disease by narrowing of the arterial lumen compromising blood flow, but also by the release of thrombi as a result of plaque erosion or rupture. (Legein et al, 2013) The endothelial cells lining the artery regulate vascular tone, where nitric oxide promotes endothelium-dependent vasodilation

through vascular smooth muscle cells, and inhibition of platelet aggregation and expression of adhesion molecules. (Pennathur & Heinecke, 2007)

Stary, 2003, classified atherogenic lesions by type according to their stage of development. (Stary, 2003) These types of lesion and the corresponding stages of development of vascular disease are illustrated in figure 2.1.

Figure 2.1 Pathogenesis of vascular disease



Activated platelets, macrophages and dysfunctional endothelial cells produce platelet derived growth factor, insulin like growth factor, thrombin, angiotensin II impair bioavailability of nitric oxide, increasing oxidative stress and endothelial dysmotility

Fatty streaks (have been observed in the aorta and coronary arteries of 20 year olds)

- Results from focal accumulation of serum lipoproteins within the intima of the vessel wall
- Contains lipid-laden macrophages, T lymphocytes and SMC
- May progress to fibrous plaque following progressive accumulation of lipids, and migration and proliferation of SMCs

As endothelial injury and inflammation progress fibro-atheroma's grow and form a plaque

- SMC proliferation results in extracellular connective tissue matrix and forms a fibrous cap that overlies a core of lipid-laden foam cells, extracellular lipid and necrotic cellular debris
- The developing plaque acquires its own microvascular network which is prone to haemorrhage and contributes to the progression of atherosclerosis
- As the plaque grows two types of vascular remodelling take place:
    - *Positive remodelling* – outward bulging of arterial wall whilst the lumen remains uncompromised
    - *Negative remodelling* – no vascular dilatation and atheroma grows inward, causing luminal narrowing.

Plaque rupture occurs due to weakening of fibrous cap by inflammatory cells:

- T lymphocytes and macrophages produce cytokines (e.g.IL-1, TNF, TNF-α) that localise to plaques which have a soft lipid core and thinner fibrous caps
- These cytokines stimulate proteolytic enzymes which degrade collagen
- T cells that accumulate at sites of plaque rupture and thrombosis also inhibit collagen synthesis
- Denudation of overlying endothelium or rupture of protective fibrous cap results in exposure of blood to the thrombogenic contents of the core of the plaque

Clinically the early stages of this process are asymptomatic, with significant arterial stenosis required prior to onset of symptomatic diseases. Vascular disease can manifest at different sites (e.g. coronary arteries, carotid arteries or peripheral arteries) with differing clinical presentations of vascular disease at the same site depending on the underlying pathology.

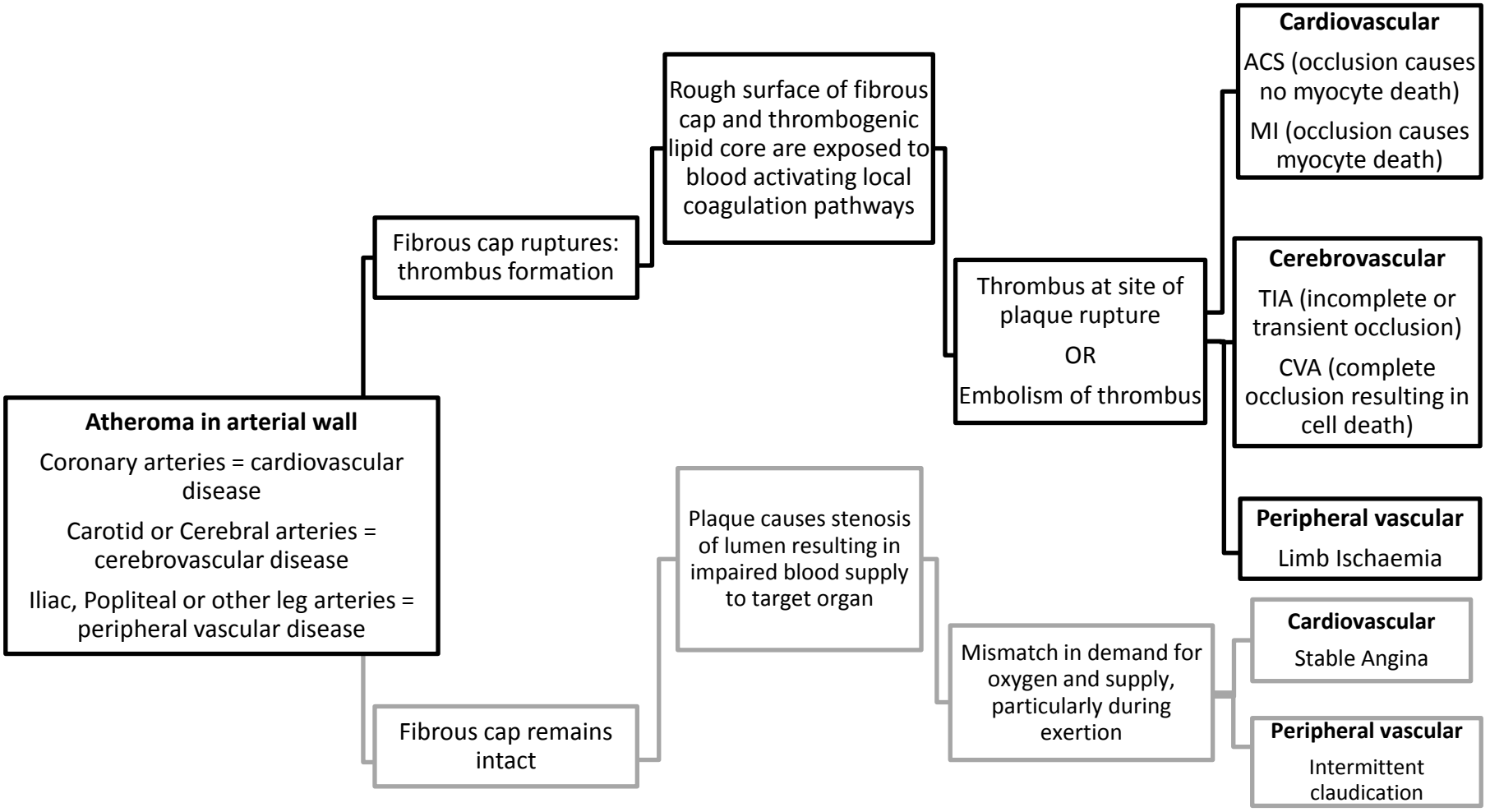
As an atherosclerotic plaque grows there is progressive luminal narrowing, blood-flow abnormalities and compromised oxygen supply to the target organ.

Disruption of the fibrous cap covering the plaque allows contact between the thrombogenic lipid core and the blood, and may result in thrombus formation, partial or complete occlusion of the vessel, or progression of the lesion by organisation of the thrombus and incorporation into the plaque. Plaque rupture is the main event that causes acute clinical presentations of myocardial infarction (MI) or acute coronary syndrome (ACS), also known as unstable angina, however severely obstructive plaques do not usually cause MI or ACS and are more strongly associated with stable angina. The reason for this is related to the way that arteries adapt to the presence of a plaque, a process known as vascular remodelling.

As shown in figure 2.1, arteries can enlarge in response to the plaque formation, and arteries which are positively remodelled (expand outwards to avoid stenosis of the lumen) are more prone to plaque rupture and clinical manifestations associated with thrombus formation, since plaque must occupy 50-70% to cause flow limitation, and the outward expansion prevents this from occurring. Those arteries which are negatively remodelled in response to atheroma formation (no outward expansion of the artery therefore allowing plaque to encroach into the

lumen) are more likely to achieve the required degree of stenosis to limit flow through the vessel and are thus more commonly associated with clinical manifestations resulting from flow limitation (e.g. stable angina) but can also be prone to plaque rupture. The relationships of these underlying processes with the clinical manifestations of vascular diseases that result are shown in figure 2.2 below.

Figure 2.2 Clinical manifestations of vascular disease according to underlying pathology



ACS = Acute Coronary Syndrome; MI = Myocardial Infarction; TIA = Transient Ischaemic Attack; CVA = Cerebrovascular Accident (“Stroke”);

2.4.2 Risk factors for vascular disease

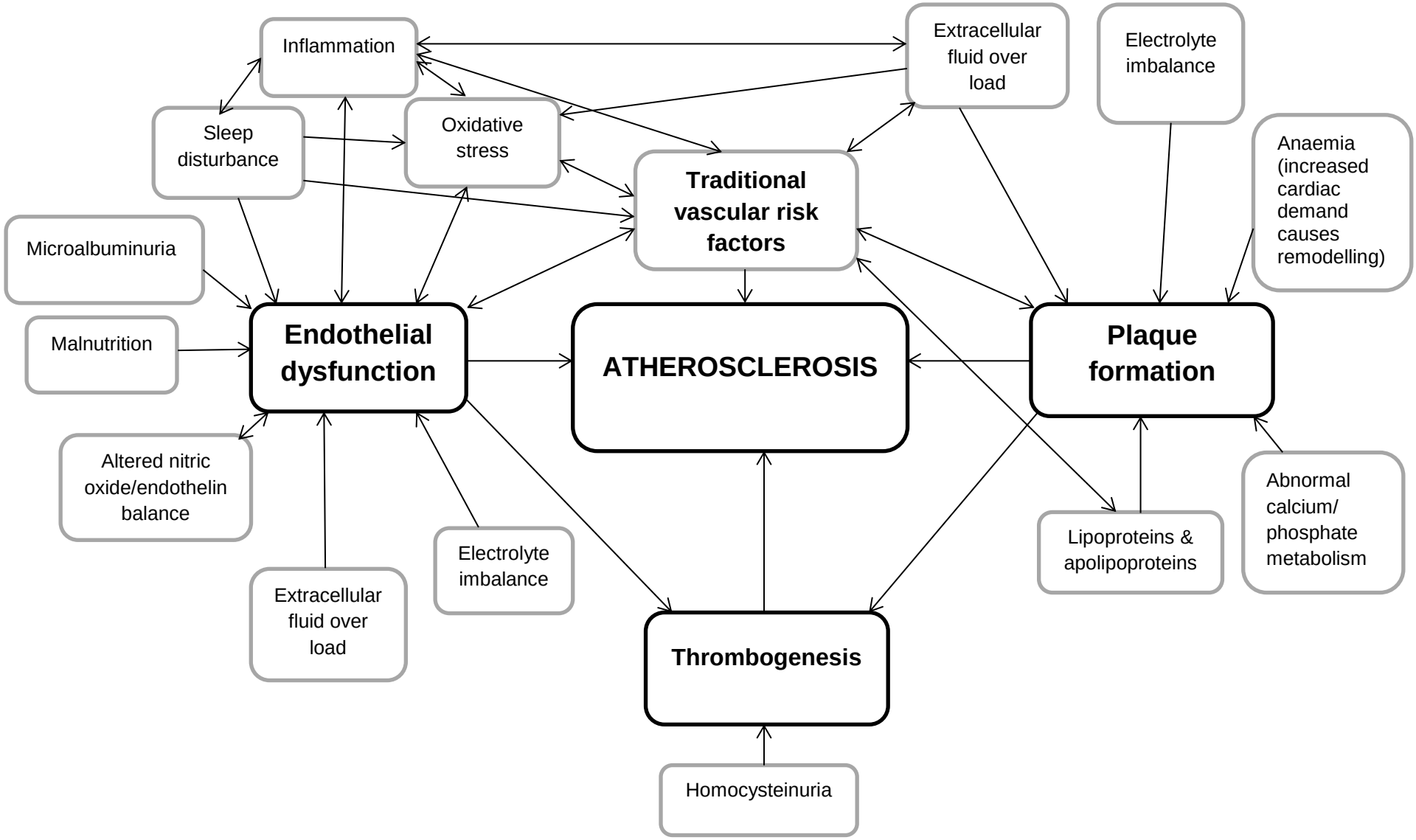
Vascular disease is known to be multi-factorial in origin and new predisposing risk factors continue to emerge. Some risk factors, such as those contributed by lifestyle choices (e.g. smoking) are considered modifiable, whilst others resulting from factors such as age or gender remain unmodifiable. Known vascular risk factors are summarised in table 2.1 below.

Table 2.1 Traditional and non-traditional cardiovascular risk factors

Traditional	Non-traditional
Hypertension	Albuminuria
Diabetes	Homocysteinuria
Kidney disease	Lipoprotein (a) and apolipoprotein (a)
Higher LDL cholesterol	Anaemia
Lower HDL cholesterol	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid overload
Physical activity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of cardiovascular disease	Inflammation
Left ventricular hypertrophy	Malnutrition
Older age	Thrombogenic factors
Male gender	Sleep disturbances
	Altered nitric oxide/endothelin balance

Adapted from: (Sarnak et al, 2003) Whilst many of these relationships, such as those between hypertension and hyperlipidaemia and cardiovascular risk have been recognised for decades, (Gordon & Kannel, 1982) as shown in table 2.1 novel risk factors continue to emerge, and although the precise interactions between these non-traditional risk factors and both traditional risk factors and the mechanisms underlying vascular disease remain unclear, some potential relationships and influences are suggested in figure 2.3 below.

Figure 2.3 Suggested interactions between traditional and non-traditional vascular risk factors and atherosclerosis



Whilst the majority of these are outside of the scope of this thesis and will not be considered further, inflammation as a novel risk factor for vascular disease will be discussed below.

2.4.3 Role of inflammation in vascular disease

Atherosclerosis is acknowledged to be an inflammatory condition. (Hansson, 2009) It has been demonstrated that vascular endothelial cells and smooth muscle cells not only respond to pro-inflammatory cytokines, in particular IL-1 and TNF, but also produce these and others as part of their response to inflammation. (Hansson, 2009) It is thought that immune activation of the artery wall may hamper plaque stability, predisposing to plaque rupture and consequent thrombi resulting in acute coronary events. (Libby & Hansson, 1991) This shared inflammatory aetiology is thought to underlie at least part of the association between systemic inflammatory conditions and atherosclerosis, although the mechanism by which the conditions are related is likely to be multifactorial and far more complex.

For reasons discussed in section 2.4.1 any reduction in endothelial bioavailability of nitric oxide will result in a proatherogenic state. (Landmesser et al, 2006) Oxidative stress, a mechanism by which bioavailability of nitric oxide is thought to be reduced by the action of oxidants, also known as free radicals or reactive oxygen species (ROS) at the vascular endothelium, (Sies & Cadenas, 1985) also plays an important role in endothelial dysfunction.

The resulting endothelial dysfunction is also known to play an important role in plaque formation and rupture by predisposing to subendothelial retention of lipids

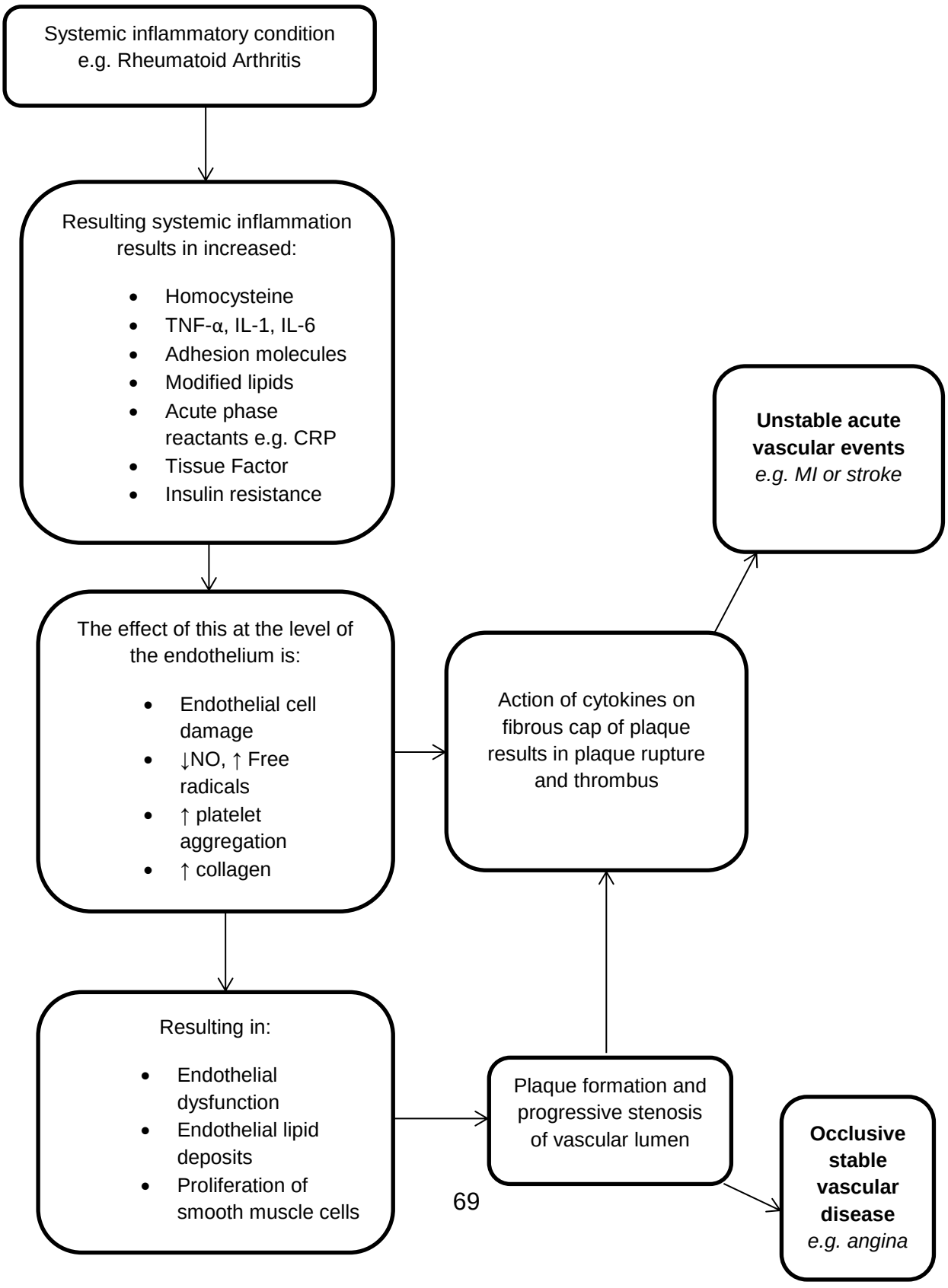
from plasma which are oxidised by free radicals, triggering the inflammatory process. The endothelium secretes chemokines and adhesion molecules resulting in the adhesion of activated platelets and white blood cells. The activated platelets and white blood cells trigger further infiltration by monocytes, which are then differentiated within the intima to become macrophages which ingest lipids to become foam cells. (Legein et al, 2013) Foam cells accumulate in the intima becoming fatty streaks which can be reversed if the inflammatory stimuli which initiated the process are reversed. However, where lipids continue to accumulate, invasion by macrophages, apoptosis and secondary necrosis of foam cells result in the development of a necrotic core and disruption to the architecture of the intima. Leaky neovascularisation can result in intraplaque haemorrhage increasing size and triggering further inflammation, and presence of collagen-rich fibrous tissue and calcification further enlarge the plaque. (Bentzon et al, 2014)

Plaque rupture occurs when the highly thrombogenic core of the plaque is exposed to the blood by a gap in its fibrous surroundings. The complete occlusion of coronary arteries by resulting thrombus can result in MI or sudden death, and incomplete or transient occlusion combined with vaso-spasm more often results in unstable angina or acute coronary syndromes. (Bentzon et al, 2014)

It has been suggested that a result of the metabolic syndrome may be the expression of adipokines by adipocytes and immune cells, and which form an important link between inflammation and metabolism. It is thought that their immunomodulatory role underpins insulin resistance, which further impairs endothelial function. (Deng & Scherer, 2010)

Potential mechanisms behind the association between inflammatory disorders are summarised in figure 2.4 below.

Figure 2.4: Mechanisms by which systemic inflammatory diseases may predispose to vascular disease



2.5 The relationship between gout and vascular diseases

There are a number of reasons why there may be an association between gout and vascular disease. These include the presence of asymptomatic hyperuricaemia prior to onset of clinical gout, the common co-existence of co-morbidities which predispose to both gout and vascular disease, such as hypertension, and finally the presence of chronic inflammation resulting in accelerated atherosclerosis. These potential mechanisms will be discussed below.

2.5.1 Hyperuricaemia and risk of vascular disease

Hyperuricaemia is known to be an independent risk factor for both cardiovascular and cerebrovascular disease. (Kim et al, 2009; Kim et al, 2010) This occurs through a mechanism of amplified oxidation of lipids and induction of cellular oxidative stress which contributes to endothelial dysfunction, resulting in decreased arterial compliance, impaired blood flow and pro-atherogenic state. (Ceriello & Motz, 2004) Studies have also demonstrated renovascular disease, renal injury and hypertension can result from this hyperuricaemic-mediated endothelial dysfunction, (Jin et al, 2012) which further contributes to vascular risk. Uric acid is also thought to have direct pro-inflammatory effects on vascular cells. (Kanellis et al, 2003; Kang et al, 2005) Studies of losartan (an angiotensin-II receptor antagonist used in hypertension) and atorvastatin (a cholesterol lowering medication) have demonstrated that a reduction of uric acid levels reduces cardiovascular risk, (Athyros et al, 2007; Høieggen et al, 2004) whilst allopurinol, the most commonly used urate lowering therapy, has been shown to improve

endothelial dysfunction, (Kanbay et al, 2011; Meléndez-Ramírez et al, 2012) blood pressure, (Kanbay et al, 2007; Kanbay et al, 2011) all-cause mortality in hyperuricaemic patients, (Luk et al, 2009) and exercise tolerance in patients with chronic stable angina. (Noman et al, 2010)

2.5.2 Co-morbidities in gout and risk of vascular disease

Many conditions known to predispose to vascular disease also predispose to gout. These include features of the metabolic syndrome, a collection of cardiovascular risk factors, defined as the presentation of three or more of:

- abdominal obesity (waist circumference >102cm for men and >88cm for women)
- triglyceride level ≥150mg/dl
- high density lipoprotein (HDL) cholesterol level < 40mg/dl for men or <50mg/dl for women
- blood pressure ≥130/85 mmHg
- fasting glycaemia ≥100 mg/dl (Grundy et al, 2004)

Increased prevalence of metabolic syndrome has been demonstrated in gout patients (44-63% in patients with gout compared to 5-25% in those without). (Choi et al, 2007a; Rho et al, 2005) Individual components of metabolic syndrome, have also been shown to predispose to gout, particularly obesity, (Bhole et al, 2010; Choi et al, 2005a; Juraschek et al, 2013b; Maynard et al, 2012) and hypertension. (Bhole et al, 2010; Choi et al, 2005a; Zhu et al, 2012)

Although diabetes appears to be protective against risk of gout, (Rodriguez et al, 2010) gout itself has been reported to increase the risk of incident type II diabetes mellitus. (Choi et al, 2008) Gout has been shown to be a risk factor for chronic kidney disease (CKD), (Teng et al, 2012; Yang et al, 2010) and similarly CKD has also been shown to be a common co-morbidity and risk factor for gout. (Soriano et al, 2011)

It is likely that these traditional vascular risk factors which commonly co-exist with gout contribute to any association between gout and vascular disease. However, the magnitude of this contribution and whether any association between gout and vascular disease persists after adjustment for these risk factors remains unclear.

2.5.3 Chronic inflammation in gout and risk of vascular disease

Since other inflammatory arthritides, such as rheumatoid arthritis, ankylosing spondylitis and other spondyloarthropathies (SpA), which do not result from hyperuricaemia, have also been associated with increased cardiovascular risk, (Avina-Zubieta et al, 2012; Gladman et al, 2009; Szabo et al, 2011) it would seem likely that inflammation plays a role in the development of vascular disease.

Mechanisms whereby inflammatory conditions lead to increased cardiovascular risk include the release of pro-inflammatory cytokines such as TNF-alpha, IL-1 and IL-6 leading to endothelial dysfunction and impaired arterial compliance. (Soltész et al, 2011)

A recent meta-analysis examining the association between individual inflammatory cytokines and vascular risk reported that a 1- standard deviation (SD) higher

baseline level for each of IL-6, IL-18, and TNF-α is associated with ~10–25% higher risk of non-fatal MI or CHD death. (Kaptoge et al, 2014) IL-6 has also been reported to be independently associated with endothelial activation in patients with RA, (Dessein et al, 2013) and systemic arterial stiffness in patients with SLE, (Barbulescu et al, 2012) and use of immunosuppressive therapies including TNF-α inhibitors, and traditional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and cyclosporine has been shown to reduce endothelial dysfunction and reduce cardiovascular risk in patients with RA, psoriatic arthropathy and SLE. (Murdaca et al, 2012)

Monosodium urate (MSU) crystals deposited in gout have been shown to strongly induce inflammation, through direct neutrophil activation and activation of the NALP3 inflammasome resulting in the release of similar pro-inflammatory cytokines, particularly IL-1, IL-6 and TNF-α, (Jin et al, 2012) during an acute attack. There is evidence that this inflammation persists between attacks, (Pascual et al, 1999; Roddy et al, 2013) and it seems likely that similar inflammatory mechanisms are at play in both RA and gout patients to result in an increased burden of vascular disease.

The idea that inflammatory activity is the major risk factor for development of subsequent cardiovascular disease has prompted the European League Against Rheumatism (EULAR) to publish recommendations for cardiovascular screening and management in inflammatory arthritis patients, (Peters et al, 2010) including an aggressive approach to managing both risk factors and inflammation. However at present, these recommendations are limited to patients with rheumatoid

arthritis, ankylosing spondylitis and psoriatic arthropathy, and do not extend to patients with gout.

2.6 Summary

This chapter has reviewed the evidence linking other inflammatory conditions with vascular disease. Common inflammatory risk factors specifically found in gout patients have also been described. In chapter 3 a systematic literature review examining the relationship between gout and vascular disease will be synthesised.

Chapter 3: Systematic Literature Review

3.1 Chapter Overview

This chapter will describe the rationale for, methods and results of a systematic review synthesising the current literature examining the relationship between gout and vascular disease.

3.2 Aims

Previous chapters have highlighted that gout is a chronic inflammatory condition, with inflammation that persists even in the asymptomatic intercritical period, (Pascual et al, 1999; Roddy et al, 2013) and that other inflammatory conditions such as RA are associated with an increased risk of vascular disease. This chapter describes the identification and synthesis of the current medical literature examining the potential association between gout and vascular disease.

3.2.1 Literature review aims

Existing systematic reviews, meta-analyses and individual studies which examine the relationship of interest will be identified. Outcomes of interest will include incidence and prevalence of, or mortality from cardiovascular, cerebrovascular or peripheral vascular disease in patients with gout.

3.2.2 Literature review objectives

The main objectives of the literature review are to establish whether there is an increased risk of cardiovascular, cerebrovascular or peripheral vascular disease in patients with gout.

Gaps in existing literature will be identified and used to inform the design of an observational study examining this relationship in more detail.

3.3 Methods

3.3.1 Medical Literature Databases

Four online bibliographic databases (MEDLINE, EMBASE, CINAHL and The Cochrane Library) were searched for relevant articles, from their creation to June 2014. These databases are described in more detail below.

3.3.1.1 MEDLINE

MEDLINE (Medical literature analysis and retrieval system Online) is compiled by the United States National Library of Medicine. It contains more than 21 million records, mainly English language journals, covering medicine and medical sciences from 1946 to the present. It uses an indexing system known as Medical Subject Heading (MeSH) terms to index entries allowing focused as well as free text searching.

3.3.1.2 EMBASE

EMBASE (Excerpta Medical Database) is compiled by the publisher Elsevier and contains over 25 million records dating from 1947 to the present. It includes biomedical and pharmaceutical content and uses an indexing system known as EMTREE to allow focused searching.

3.3.1.3 CINAHL

CINAHL (Cumulative Index to Nursing and Allied Health Literature) is compiled by EBSCO publishing and contains over 2.6 million records from 1981 to the present. Its content includes nursing, biomedical and allied health disciplines. CINAHL uses a thesaurus for focused searching adapted from the MeSH terms used by MEDLINE.

3.3.1.4 The Cochrane Library

The Cochrane Library is a collection of six databases, including the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database and the NHS Economic Evaluation Database. Its aim is to make the results of well-designed controlled trials and systematic reviews easily available in order to inform healthcare decisions. It is published by Wiley Online, and is free to all UK residents.

3.3.2 Search strategy

MEDLINE, EMBASE, CINAHL and the Cochrane Library were each searched using a combination of free-text and MeSH (or database-specific equivalent) headings. The search terms used are described in more detail below.

3.3.3 Search Terminology

The search strategy aim was to create a literature search broad enough to include all papers on the association of interest, but narrow enough to exclude the majority of irrelevant results. The selection of search terms is described in this section.

3.3.3.1 Condition of Interest – Gout

"Gout" was searched separately in both free-text and MeSH (or database-specific equivalent) terms. MeSH headings were "exploded" to broaden their definition. This would result in the inclusion of similar terms such as "gouty arthritis" in the search. These separate searches were then combined by use of the Boolean operator "or".

3.3.3.2 Outcome of Interest – Vascular Disease

MeSH, CINAHL and EMTREE terms were identified for various forms of vascular disease. The most common vascular diseases including "angina pectoris", "myocardial infarction" (MI), "cerebrovascular accident" (CVA) and "transient ischaemic attack" (TIA) as well as the lay terms commonly used for these conditions such as "heart attack" and "stroke" were initially used to interrogate the

database-specific indexing trees to identify search terms related to those diseases. From this, more general organ-system based terms, “cardiovascular disease”, “cerebrovascular disease” and peripheral vascular disease” were used to identify other less specific but important descriptors that may broaden the search. These terms were also “exploded” in order to broaden their definition. Free text searching was also performed, using complete and truncated versions of the search terms identified, allowing similar terms such as ischaemic and ischaemia to be returned by the same search term. These searches were combined with the MeSH searches using the Boolean operator “or”.

3.3.3.3 Study design – Observational

Observational studies were selected as the most appropriate design by which to compare vascular outcomes between groups of gout and non-gout patients, since there may be a considerable time between incidence of the exposure (gout) and development of the outcome of interest (vascular disease). MeSH, EMTREE and CINAHL terms were identified and exploded in order to broaden their search definition. Free text searching was also performed and the searches finally combined using the Boolean operator “or”.

3.3.4 Search Term Combination and Search Limits

Searches were performed for the exposure (gout), outcome (vascular disease) and design terms as detailed in section 3.3.3 above, and then combined using the Boolean operator “and”. This process was undertaken three times with the outcome included being a different type of vascular disease each time,

cardiovascular the first, cerebrovascular the second and peripheral vascular disease the final time. Searches were limited to human studies only. No other limits were applied.

The detailed search strategies can be found in Appendix 1.

3.3.5 Inclusion and exclusion criteria

Potential title/abstracts, and/or full text articles were independently assessed to determine inclusion or exclusion by the author and another reviewer, Dr Priyanka Chandratre (Clinical Research Training Fellow & Honorary Specialist Registrar in Rheumatology).

To be eligible for inclusion, studies must have met all of the following criteria;

1. *Exposure of interest:* studies must report on patients with gout, or a subset of patients with gout.

2. *Outcome of interest:* studies must report the incidence or prevalence of vascular disease, or mortality from vascular disease.

3. *Study design:* studies must compare the outcomes of interest between gout patients and a control group, or statistics based upon the general population.

Studies were excluded from the review if they met any of the following criteria;

1. *Exposure of interest* – studies reporting other diseases, or studies examining patients with hyperuricaemia, without a subgroup of patients with gout.

2. *Outcome of interest* – studies with outcomes other than those specified by the inclusion criteria.

3. *Article type* – papers other than those reporting on observational studies, for example case studies, editorials or clinical guidelines.

4. *Full text not available* - every effort was made to obtain the full text of all relevant articles identified, including applications to the British Library for papers that could not be accessed elsewhere, those that could not be obtained through the British Library were excluded

5. *Foreign language translation* – where English translations were not available, translators working within the Research Institute for Primary Care & Health Sciences, Keele University were utilised, and foreign language papers where a translator was not available within the department were excluded.

Full text review was undertaken for any title/abstract that did not clearly meet either the inclusion or exclusion criteria.

In addition, full text review was undertaken for;

> Any title/abstract which met all inclusion criteria except for specifically identifying gout (but that did identify hyperuricaemia) to ascertain any subgroups of gout patients.
>
> Any title/abstract which appeared to report all-cause mortality to ascertain any report of vascular mortality.

When multiple articles were published from a single study, reports that contained the most complete and relevant data on the association between gout and vascular disease were selected.

Disagreement was resolved by consultation with a third reviewer (Dr Samantha Hider, PhD supervisor, Senior Lecturer in Rheumatology and Honorary Consultant Rheumatologist).

3.3.6 Reference Search

The reference sections of each paper identified as meeting the inclusion criteria detailed in section 3.3.5 were screened to ensure no relevant references were missed. This screening was performed by the same process as that for the studies identified from the medical database search.

3.4 Quality assessment

All included articles were assessed for quality by the author and second reviewer Priyanka Chandratre (Clinical Research Training Fellow & Honorary Specialist Registrar in Rheumatology) using an adaptation of a previously validated quality assessment tool. (Wells et al, 2000)

3.4.1 Quality assessment tool design

Prior to full review of the included papers, established quality assessment tools were reviewed and adapted to include questions specific to the study of gout.

The final version combines quality assessment points from the Newcastle-Ottawa Scale (NOS), (Wells et al, 2000) recommended for use in systematic reviews of observational studies by the Cochrane Collaboration, with one supplementary point from a tool by Altman, (Altman, 2001) and one developed by the author. The supplementary points added assess whether the appropriate statistical methods were used, (Altman, 2001) and how the study accounts for patients with asymptomatic hyperuricaemia (author-defined). The latter was included as it was considered important to treat patients with asymptomatic hyperuricaemia separately to those with clinical gout because although asymptomatic hyperuricaemia is the biochemical precursor to gout, only a minority of hyperuricaemic patients go on to develop clinical gout, and by definition asymptomatic hyperuricaemic patients lack the inflammatory response triggered by deposition of MSU crystals thought to contribute to risk of vascular disease.

The quality assessment tool used, along with a detailed description of the origins of the individual quality assessment points is given in table 3.1

Table 3.1 Quality Assessment criteria

Criteria Number	Review criteria	Awarded	Not awarded	Origin
	Selection			
1.	Are the gout patients in the study likely to be representative of the total gout population?	Yes	Unlikely or not described	NOS
2.	Are the non-gout patients (or mortality statistics) from the same population as the gout patients?	Yes	No or not described	NOS
3.	How was gout/non-gout status ascertained?	Secure record or standardised interview/clinical assessment	Self-report or not described	NOS
4.	Does the study demonstrate that the outcomes of interest (to this review) were not present at the start of the study?	Yes	No or not described	NOS
	Comparability			
5.	Study controls for age and sex?	Yes	No or not described	NOS
6.	Study controls for other predictors of CVD or mortality? (diabetes, hypertension, BMI, hyperlipidaemia, smoking status)	Yes	No or not described	NOS
	Outcomes			
7.	How was outcome assessed?	Independent blind assessment or record linkage	Self report or not described	NOS
8.	Was follow up long enough for outcomes to occur?	Greater than 2 years	Less than 2 years or not described	NOS
9.	How adequate was follow-up of cohorts? (<30% loss to follow up)	Yes (can be assumed for retrospective studies)	No or not described	NOS
	Analysis			
10.	Was the analysis of data appropriate?	Appropriate methods used	Appropriate methods not used or methods not described	Altman*
11.	How well does the study account for patients with hyperuricaemia?	Excludes hyperuricaemia patients, analyses pure gout as a separate group or analyses data with development of hyperuricaemia as a possible predictive variable	Does not exclude hyperuricaemia patients or does not account for them in the analysis	Author-specified
NOS = Newcastle Ottawa Scale (Wells et al, 2000) *(Altman, 2001)				

3.4.2 Quality Assessment of Studies

Quality assessment was performed independently, and agreement reached with a second reviewer, Dr Priyanka Chandratre (Clinical Research Training Fellow & Honorary Specialist Registrar in Rheumatology). Disagreements were discussed and if necessary decided by a third reviewer, Dr Samantha Hider, PhD supervisor, Senior Lecturer in Rheumatology & Honorary Consultant Rheumatologist. Agreement was reached on quality assessment score in 100% of cases.

3.5 Data extraction

Included articles were also read by another reviewer, Dr Priyanka Chandratre (Clinical Research Training Fellow & Honorary Specialist Registrar in Rheumatology) and data tabulated into a purpose-designed form. Data was collected on gout and control population number and source, duration of follow-up, loss to follow-up, definition of gout used, average age and gender distribution of the study population, information on previous vascular disease or vascular risk factors and outcomes.

3.6 Data analysis

Pooled estimates of hazard ratios (HRs) were calculated using the DerSimonian and Laird random effects model, (DerSimonian & Laird, 1986) for mortality from any cardiovascular disease and coronary heart disease, and incidence of coronary heart disease. This technique weights individual studies according to the precision of each study estimate, giving a pooled estimate and 95% confidence interval. A random effects model was chosen due to the likelihood of heterogeneity between studies. Measuring the inconsistency of studies' results was considered using Cochran's Q test and the I^2 statistic. The former is the classical measure of heterogeneity which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. The latter I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance. (Higgins & Thompson, 2002)

Data for the prevalence of cardiovascular diseases, mortality from myocardial infarction, and incidence of any cardiovascular disease and MI were unsuitable for meta-analysis due to heterogeneity in study design and outcomes measured, and are thus narratively described.

Differences between the studies and their characteristics, including having met or not met the quality assessment criteria and the geographical location, population size and gender distributions of the study populations were compared using Fisher's Exact Test, a statistical test used to compare categorical data, particularly

where sample sizes are small. (Fisher, 1922) Statistical analysis was performed using Stata statistical software release 12 (StataCorp: College Station, TX, 2011)

3.7 Assessment of Publication Bias

Publication bias refers to the suggestion that studies with statistically significant findings are more likely to be published than those with negative findings, particularly in large English language journals and those indexed in online electronic databases such as Medline and Embase. (Juni et al, 2002) Presence of publication bias was assessed using funnel plot, Begg's and Egger's tests, (Begg & Mazumdar, 1994; Egger et al, 1997) described below.

3.7.1 Use of funnel plots in detection of publication bias

Plots of sample size against effect size, called funnel plots because they are commonly of the appearance of a symmetrical inverted funnel, can be used to detect publication bias. (Egger & Smith, 1995; Light & Pillemer, 1984) The funnel shaped appearance is created since, if precision of the effect estimate is increased as sample size of the included studies increases, results from smaller studies scatter widely at the bottom of the graph, with larger studies plotting closer together towards the top of the graph. Therefore presence of bias will result in an asymmetrical or skewed plot to visual inspection. (Sterne & Egger, 2001) However, numerical methods of detecting asymmetry in funnel plots have also been proposed, such as the eponymous Egger's and Begg's tests. (Begg & Mazumdar, 1994; Egger et al, 1997) In this thesis I present assessment of

publication bias using both Begg's and Egger's test and these are described in more detail below.

3.7.2 Begg's Test

Begg's test is used to identify evidence of publication bias in meta-analyses by looking for correlation between the individual study estimates and meta-analysis weight, i.e. whether the study estimate is related to the study size. (Begg & Mazumdar, 1994) However, the variance is not the same at all points, and in order to account for this, the pooled estimate is subtracted from each individual study estimate, and the result divided by the standard error. This results in estimates with a similar variance, and Kendall's rank correlation coefficient is used to test a correlation between deviation divided by standard error and the study weight (equivalent to study size). However, where there are few studies included in a meta-analysis Begg's test has little power to detect publication bias. (Sterne et al, 2002) Although Begg's test makes fewer assumptions than Egger's test, it is insensitive to many types of bias that Egger's test will detect.

3.7.3 Egger's Test

Egger's test approaches the problem of publication bias slightly differently, using linear regression to estimate the relationship between the effect size divided by its standard error, (also called the standard normal deviate), and the inverse standard

error. The inverse standard error for small samples should be close to zero (since standard error is dependent on sample size), and so even where small studies estimate large effect sizes, the standard normal deviate will be small since the standard error with be large, with the reverse being true for larger studies. (Egger et al, 1997) In the absence of funnel plot asymmetry indicating publication bias, then the intercept from the unweighted logistic regression should be zero. Thus the further from zero the intercept, the greater the asymmetry and therefore the greater the indicator of publication bias.

3.8 Results

Following the systematic literature searches summarised in Figure 3.1-3.3 14 papers examining the association between gout and cardiovascular disease were included, 2 papers examining gout and cerebrovascular disease, and 2 papers examining gout and peripheral vascular disease.

3.8.1 Summary of Search Results

A flowchart showing the number of articles identified by the search strategy and their subsequent inclusion or exclusion in the final review can be found in Figures 3.1- 3.3 with the results for cardiovascular, cerebrovascular and peripheral vascular disease displayed separately.

Figure 3.1 Summary of systematic review article search process for gout and cardiovascular Disease

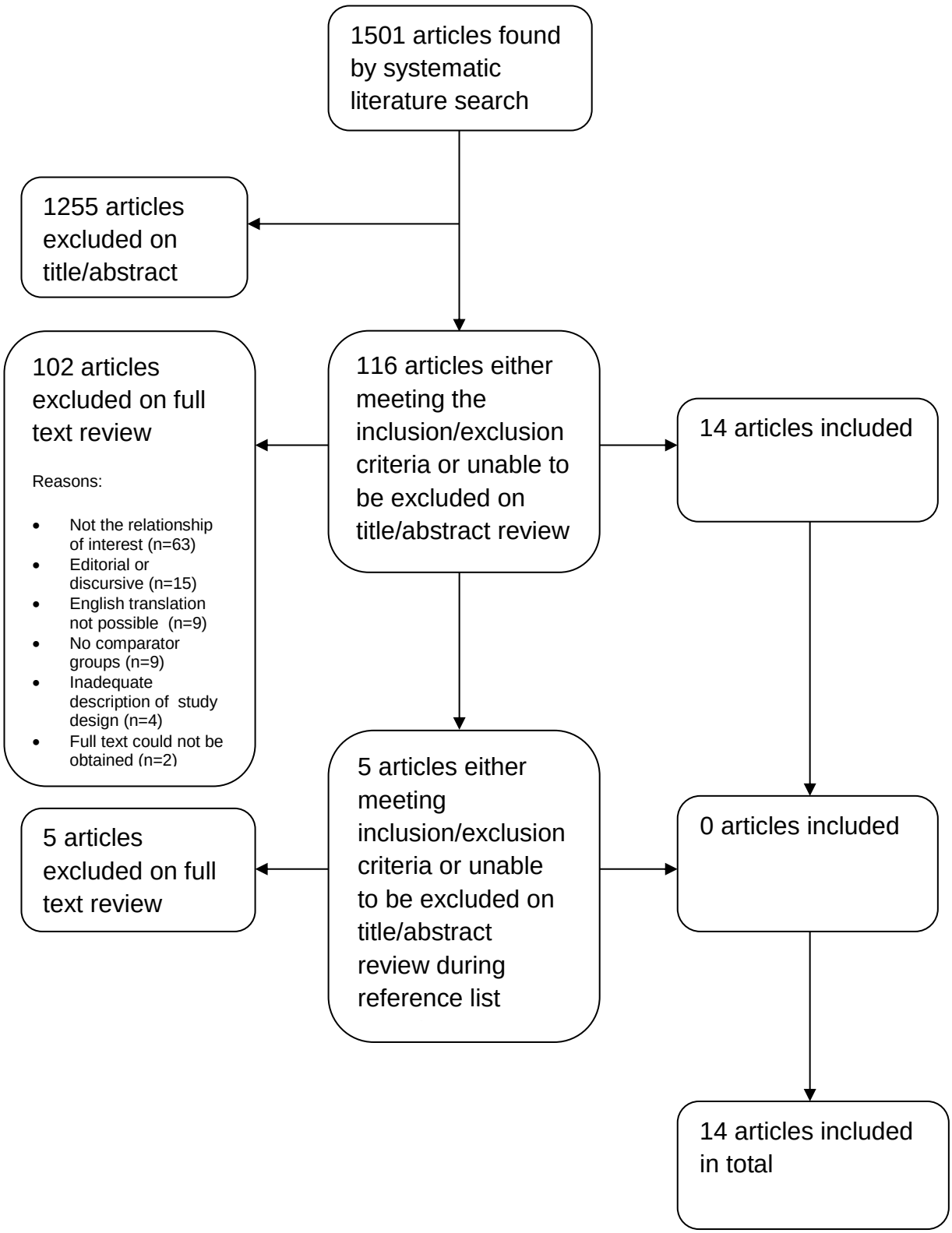


Figure 3.2 Summary of systematic review article search process for gout and cerebrovascular disease

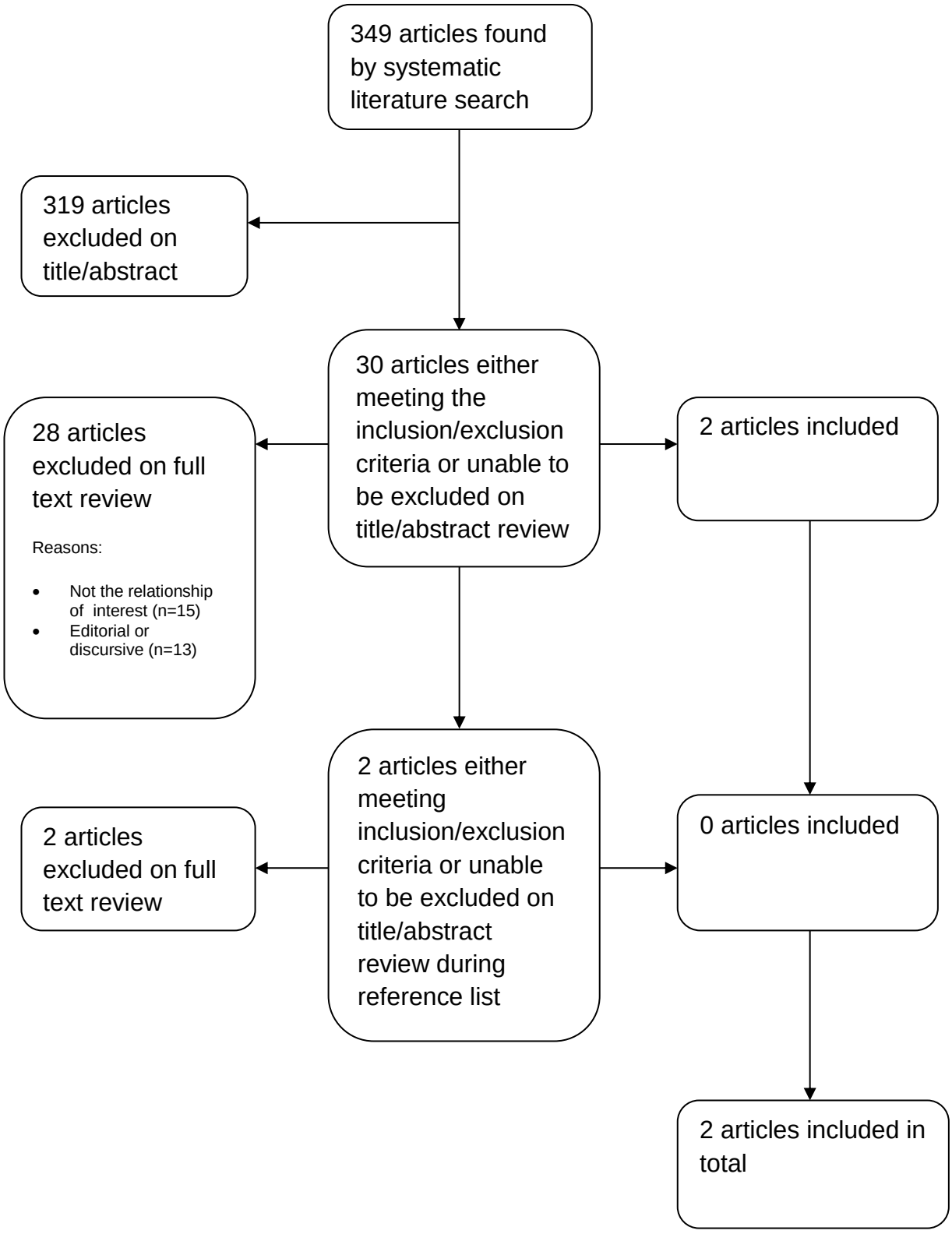
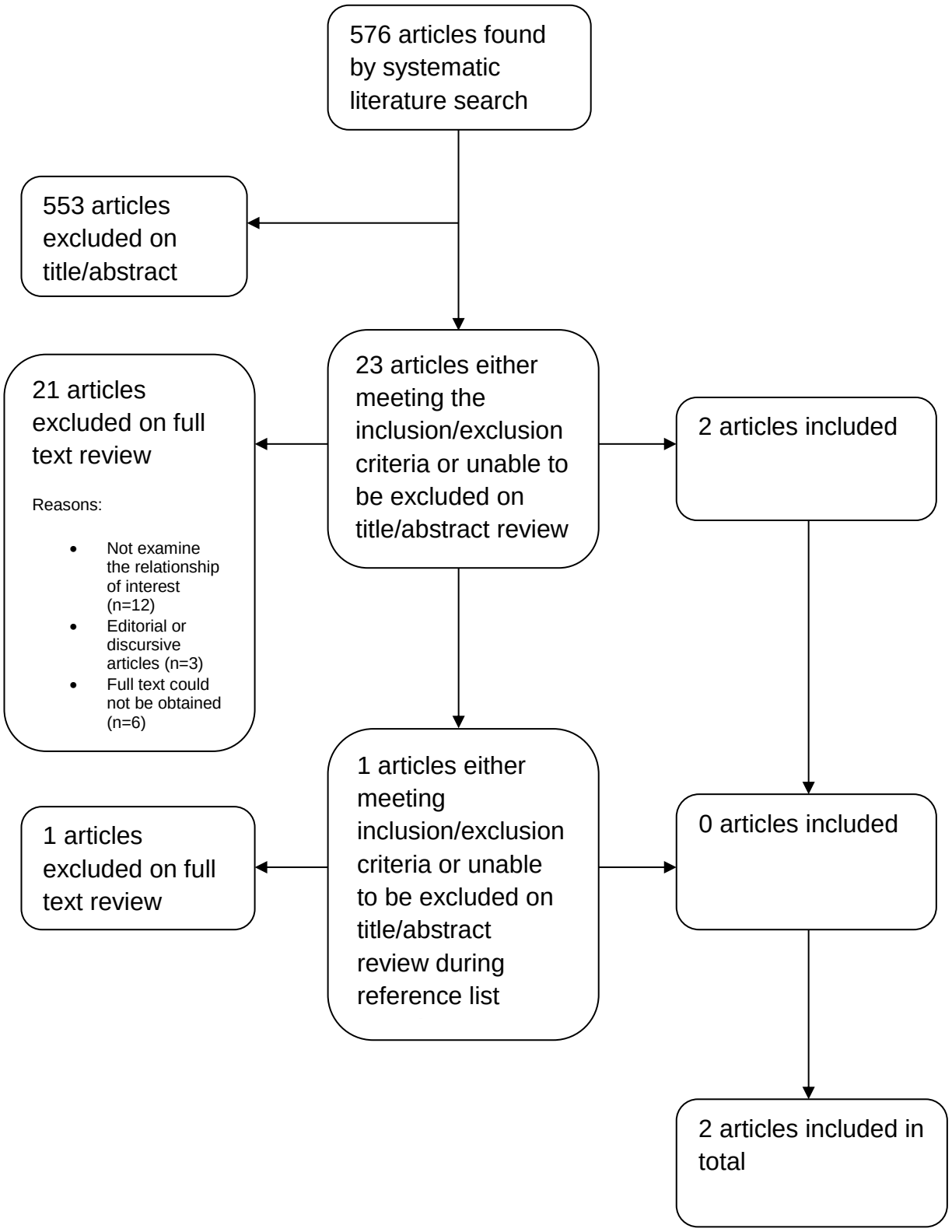


Figure 3.3 Summary of systematic review article search process for gout and peripheral vascular disease



Two studies report the relationship between gout and cerebrovascular disease, one reports mortality from cerebrovascular disease, (Teng et al, 2012) and the other incidence of stroke. (Seminog & Goldacre, 2013)

Of 2 articles identified to report on gout and peripheral vascular disease (PVD), 1 reported on incidence of PVD, (Baker et al, 2007) and 1 on prevalence of PVD. (De Muckadell & Gyntelberg, 1976)

Table 3.2 shows the quality assessment of the included studies.

Table 3.2 Quality assessment of included studies

Author	Type of vascular disease investigated	Quality Assessment Criteria											Total Score
		1	2	3	4	5	6	7	8	9	10	11	
Abbott	Cardiovascular	1	1	1	1	0	1	1	1	0	1	1	9
Baker	PVD	0	1	0	1	1	1	1	1	1	1	1	9
Choi & Curhan (b)	Cardiovascular	0	1	0	1	1	1	1	1	1	1	1	9
De Vera	Cardiovascular	1	1	1	1	0	1	1	1	1	1	1	10
Gelber	Cardiovascular	0	1	0	1	0	1	1	1	1	1	1	8
Janssens	Cardiovascular	1	1	1	1	1	1	1	1	1	1	1	11
Kok	Cardiovascular	1	1	1	1	1	1	1	1	N/A	1	1	10
Krishnan 2006	Cardiovascular	0	1	1	1	1	1	1	1	1	1	1	10
Krishnan 2008	Cardiovascular	0	1	1	1	1	1	1	1	0	1	1	9
Kuo 2010	Cardiovascular	1	1	0	1	1	1	1	0	0	1	1	8
Kuo 2013	Cardiovascular	1	1	1	1	1	1	1	1	N/A	1	1	10
Mikuls	Cardiovascular	1	1	1	0	1	0	1	N/A	N/A	1	1	7
Novak	Cardiovascular	1	1	1	0	1	0	1	N/A	N/A	1	1	7
Schaffalitzky de Muckadell	Cardiovascular PVD	1	1	0	0	1	0	1	N/A	N/A	1	1	6
Seminog & Goldacre	Cardiovascular Cerebrovascular	0	1	1	1	1	1	1	1	N/A	1	1	9
Stack	Cardiovascular	1	1	1	0	1	1	1	1	0	1	1	9
Teng	Cardiovascular Cerebrovascular	1	1	1	1	1	1	1	1	1	1	1	11

Table 3.3: Included Articles study population and follow-up information

Author	Year	Type of vascular disease investigated	Location	Gout Population (number and source)	Control Population	Average Follow-up Length (years)	Loss to Follow up
Abbott et al	1988	Cardiovascular	USA	n=113 community	n=4188 community	With gout M=7.3, F=8.0 Without gout M=7.6, W=8.4	Not described
Baker et al	2007	PVD	USA	n=1485 community	n=11343 community	10.5	Less than 10%
Choi & Curhan	2007	Cardiovascular	USA	n=2280 community	n=44978 community	12	6% per 2y cycle
Devera	2010	Cardiovascular	Canada	n=9642 community	n=48210 community	7	Not described
Gelber et al	1997	Cardiovascular	USA	n=106 community	n=1518 community	MH cohort 30 JH cohort 33	5%
Janssens et al	2003	Cardiovascular	Holland	prevalence study n=261 case-control n=170 community	first part 522 2nd n=340 community, age-, sex-, practice-matched	11.1	Not described
Kok	2012	Cardiovascular	Taiwan	n=164436 community	n=3694377 community	Not stated	N/A
Krishnan et al	2006	Cardiovascular	USA	n=1123 community	n=11743 community	6.5	Not described
Krishnan et al (Uses sample of population used by Krishan et al, 2006)	2008	Cardiovascular	USA	n=655 community	n=8450 community	17	Not described
Kuo et al	2010	Cardiovascular	Taiwan	n=1311 community	n=48021 community	4.75	Not described
Kuo et al	2013	Cardiovascular	Taiwan	n= 704503 community	n=677947 community	8	N/A
Mikuls et al	2005	Cardiovascular	UK	n=56483 community	n=150867 OA community patients –	10	Not applicable

Table 3.3: Included Articles study population and follow-up information

Author	Year	Type of vascular disease investigated	Location	Gout Population (number and source)	Control Population	Average Follow-up Length (years)	Loss to Follow up
					not matched		
Novak et al	2007	Cardiovascular	US	n=1171 community	n=58550 "matched" age, gender, race community	N/A: Prevalence at index date	Not applicable
Schaffalitzky de Muckadell & Gyntelberg	1976	Cardiovascular PVD	Denmark	n=104 community	n=208 community, age-matched	1	9.5%
Seminog & Goldacre	2013	Cardiovascular Cerebrovascular	England	n=205207 hospital	n=7673635 hospital	3.8 HES dataset 5.7 ORLS dataset	N/A
Stack	2014	Cardiovascular	USA	n=468 community	n=15304 community	10	N/A
Teng et al	2012	Cardiovascular Cerebrovascular	Singapore	Sub-population with no prior history of vascular disease n=1736 community	n= 45299 community	8.1	17.3%

CPRD = Clinical Practice Research Datalink; F= female; HES= Hospital Episode Statistics; JH=Johns Hopkins Hospital; M=male; MH= Meharry Hopkins Hospital; N/A= not applicable; OA = osteoarthritis; ORLS= Oxford Record Linkage Study; PVD=peripheral vascular disease; y=year

3.8.2 Gout and cardiovascular disease

3.8.2.1 Gout and prevalence of cardiovascular disease

Four studies were identified reporting prevalence of cardiovascular disease in patients with gout compared to those without (with a combined population of 58019 gout patients and 210151 non-gout patients). Two were retrospective cohort studies using electronic medical records, one from Europe and one from the US; one was a cross-sectional survey from Denmark, and one a case-control study from Holland. (De Muckadell & Gyntelberg, 1976; Janssens et al, 2003; Mikuls et al, 2005b; Novak et al, 2007)

The two cohort studies and cross-sectional survey reported a statistically significant increased prevalence of cardiovascular disease, (De Muckadell & Gyntelberg, 1976; Mikuls et al, 2005b; Novak et al, 2007) whilst the case-control study did not. (Janssens et al, 2003) The studies differ not only by design but also by the types of cardiovascular disease used as events of interest, with one reporting prevalence of any cardiovascular disease, (Janssens et al, 2003) two reporting prevalence of coronary artery disease, (Mikuls et al, 2005b; Novak et al, 2007) two prevalence of MI, (De Muckadell & Gyntelberg, 1976; Novak et al, 2007) and one prevalence of angina. (De Muckadell & Gyntelberg, 1976) The findings reported are summarised in table 3.4.

Table 3.4 Studies reporting prevalence of cardiovascular disease

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor data	Outcomes
Prevalence of any cardiovascular disease					
Janssens et al, 2003	ICHPPC-2 codes	Not described	Gout=91 Not gout=68	2 parts – prevalence of CV diseases and then those without were followed up	% prevalence • Gout group =26% • Controls = 21% • Difference not statistically significant
Prevalence of coronary heart disease					
Mikuls et al, 2005	CPRD coded (OXMIS codes)	Gout=60.5 Not gout=66.8	Gout=79.6 Not gout=33.8	Not collected and therefore not excluded – adjusted for age and sex	• COR 1.34 (1.31-1.37) • AOR 1.75 (1.70-1.79)
Novak et al, 2007	ICD code-physician recorded	Gout group 45.9 No gout group 40.4	Gout group 85.0% No gout 54.3%	Preindex data not collected – not adjusted	% prevalence • Gout group = 7.26% • No gout = 3.53% • p≤0.05 for difference
Schaffalitzky de Muckadell & Gyntelberg, 1976	Patient recall of physician diagnosed gout	Not described – all between 40 and 59	100	Not described	% prevalence Angina • Gout group = 11.5% • No gout = 2.4% • p=<0.001 for difference
Prevalence of MI					
Novak et al, 2007	ICD code-physician recorded	Gout group 45.9 No gout group 40.4	Gout group 85.0% No gout 54.3%	Preindex data not collected – not adjusted	% prevalence AMI • Gout group 0.51% • No gout = 0.35% • No significance levels are reported
Schaffalitzky de Muckadell & Gyntelberg, 1976	Patient recall of physician diagnosed gout	Not described – all between 40 and 59	100	Not described	% prevalence • Gout = 2.9% • No gout = 1.4% • Difference not statistically significant

AMI = acute myocardial infarction; AOR = adjusted odds ratio; CHD = coronary heart disease; COR = crude odds ratio; CPRD = clinical practice research datalink; CV= cardiovascular; ICD = International Classification of Diseases; ICHPPC= International Classification of Health Problems in Primary Care, OXMIS = Oxford Medical Information Systems

3.8.2.2 Gout and incidence of cardiovascular disease

Eight studies were identified reporting incidence of cardiovascular disease in patients with gout compared to those without (923,235 gout patients and 8,462,741 non-gout patients). Four were prospective cohort studies from the US, (Abbott et al, 1988; Choi & Curhan, 2007; Gelber et al, 1997; Krishnan et al, 2006) three were retrospective cohort studies using healthcare records from Canada, Taiwan and the UK, (De Vera et al, 2010; Kuo et al, 2013; Seminog & Goldacre, 2013) and one a case-control study from Holland. (Janssens et al, 2003)

These studies also differed in the types of incident cardiovascular disease investigated and reported conflicting results. One study was identified which reported incidence of any cardiovascular disease, (Janssens et al, 2003) two which reported incidence of coronary heart disease, (Abbott et al, 1988; Gelber et al, 1997) one reporting incidence of angina, (Abbott et al, 1988) and six incidence of MI. (Abbott et al, 1988; Choi & Curhan, 2007; De Vera et al, 2010; Krishnan et al, 2006; Kuo et al, 2013; Seminog & Goldacre, 2013) The results will be presented grouped according to the types of incident cardiovascular disease investigated.

Janssens et al, 2003 did not find an increased risk of any type of cardiovascular disease (which included stroke), and Gelber et al, 1997 did not find any increased risk of incident coronary heart disease in their population of male healthcare professionals with gout compared to those without. (Gelber et al, 1997; Janssens et al, 2003) In contrast, Abbott et al, 1987, did report a statistically significant increased risk of both coronary heart disease and angina in their male participants

with gout compared to those without, but not their female participants (although the number of female participants was extremely small n=19). (Abbott et al, 1988)

The details reported in these studies are presented in table 3.5

Table 3.5 Studies investigating gout and incidence of cardiovascular disease

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Incidence of any cardiovascular disease					
Janssens et al, 2003	ICHPPC-2 codes	Not described	Gout=91 Not gout=68	2 parts – prevalence of CV diseases and then those without were followed up	Risk ratio 0.98 (N.S)
Incidence of coronary heart disease					
Abbott et al, 1988	Self report	Gout M=53.3/F=58.7 Not gout M=54.6/F=55.3	Gout =83% Not gout = 42% Total = 43%	Excluded if prior HTN and CVD: adjusted for age, BP, total cholesterol level, alcohol consumption, BMI, DM	Men – Coronary Heart Disease • CHR 1.6 (1.1-2.2) • AHR 1.6 (1.1-2.5) Men - Angina • CHR 1.9 (1.2-3.1) • AHR1.8 (1.1-3.2) Women No statistically significant relationships
Gelber et al, 1997	Self report – ACR survey gout criteria	Meharry Hopkins Cohort =29 Johns Hopkins Cohort =26	100	Excluded if prior CHD: adjusted for serum cholesterol, BMI, smoking, alcohol, DM, HTN	• CHR 0.85 (0.40-1.81) • AHR 0.59 (0.24-1.46)
ACR = American College of Rheumatology; AHR = adjusted hazard ratio; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHR = crude hazard ratio; CV = cardiovascular ; CVD = cardiovascular disease; DM = diabetes mellitus; HR= hazard ratio; HTN = hypertension; ICHPPC= International Classification of Health Problems in Primary Care; NS = non-significant;					

Thus only the studies investigating incident coronary heart disease were appropriate for meta-analysis and this was undertaken using both the fixed and random effects model. (Abbott et al, 1988; Gelber et al, 1997)

The results of this meta-analysis are shown below in Tables 3.6 and 3.7 presented as the crude results (table 3.6) followed by the adjusted results (table 3.7) and Figures 3.4 and 3.5. Due to the likelihood of heterogeneity between studies, the DerSimonian and Laird random effects model was more appropriate. The pooled estimate of the HR was 1.28 (95%CI[0.71-2.31]) for the crude results, and for the adjusted results was 1.08 (95%CI[0.09-2.07]). No statistically significant excess risk of incidence of coronary heart disease was demonstrated.

Table 3.6: Study effect sizes and weights in meta-analysis of crude results of studies examining the relationship between gout and incidence of coronary heart disease

Authors	Hazard Ratio	95% CI	% Weight
Abbott et al, 1987	1.60	1.10-2.20	64.6%
Gelber et al, 1997	0.85	0.40-1.81	35.4%
D&L Pooled Effect Size	1.28	0.71-2.31	100.0%
CI= confidence interval; D&L = DerSimonian & Laird			

I^2 = 55.1% which reflects moderate heterogeneity, but Cochran's Q test yielded p=0.14, suggesting no significant heterogeneity.

Table 3.7: Study effect sizes and weights in meta-analysis of adjusted results of studies examining the relationship between gout and incident coronary heart disease

Author	Hazard Ratio	95% CI	% Weight
Abbott et al, 1987	1.60	1.10-2.50	58.4
Gelber et al, 1997	0.59	0.24-1.46	41.6
D&L Pooled Effect Size	1.06	0.40-2.77	100%
CI= confidence interval; D&L = DerSimonian & Laird			

I^2 = 74.3% which reflects significant heterogeneity, but Cochran's Q test yielded p=0.05 suggesting no significant heterogeneity.

Figure 3.4: Meta-analysis of crude findings of studies examining the relationship between gout and incidence of coronary heart disease

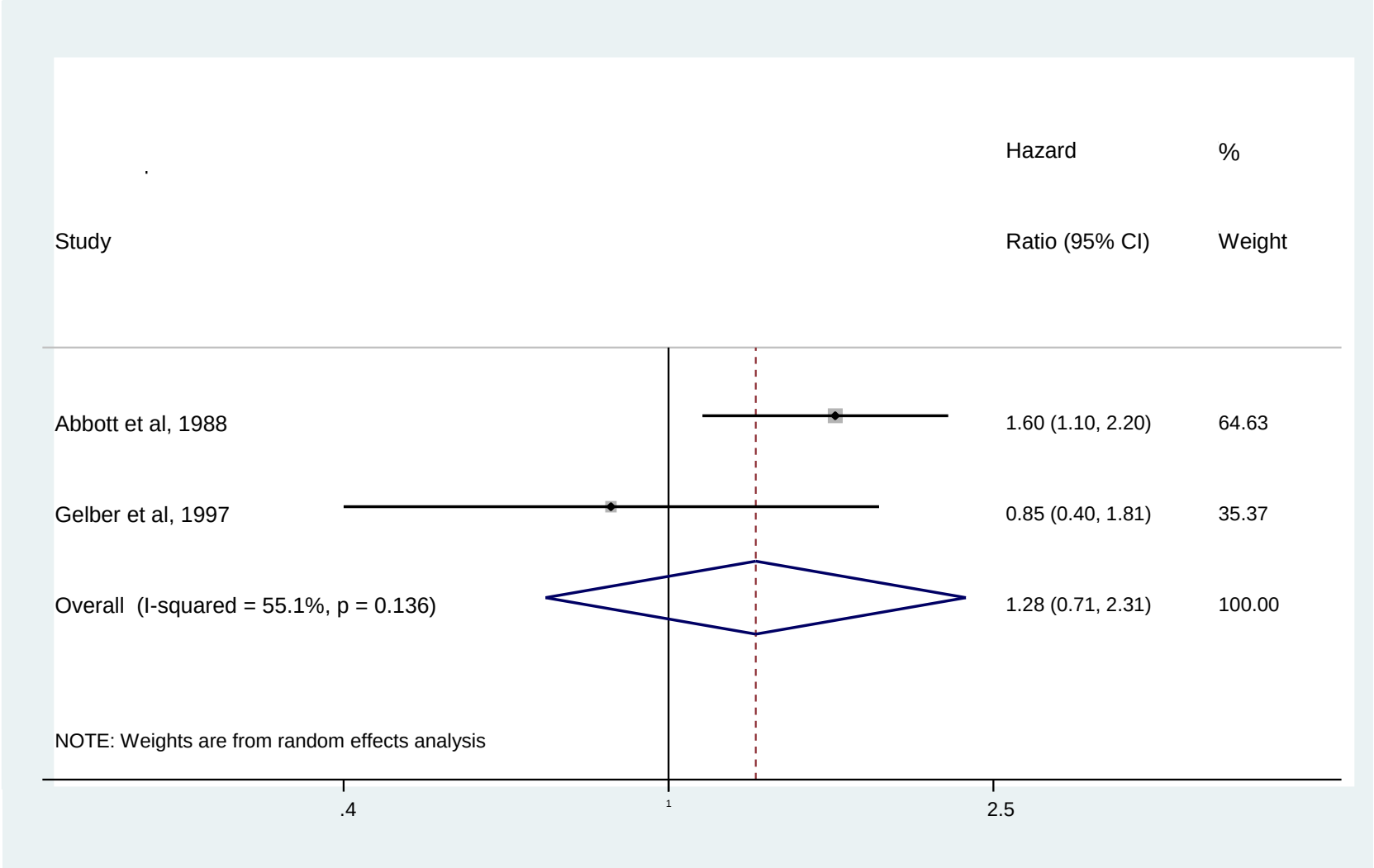
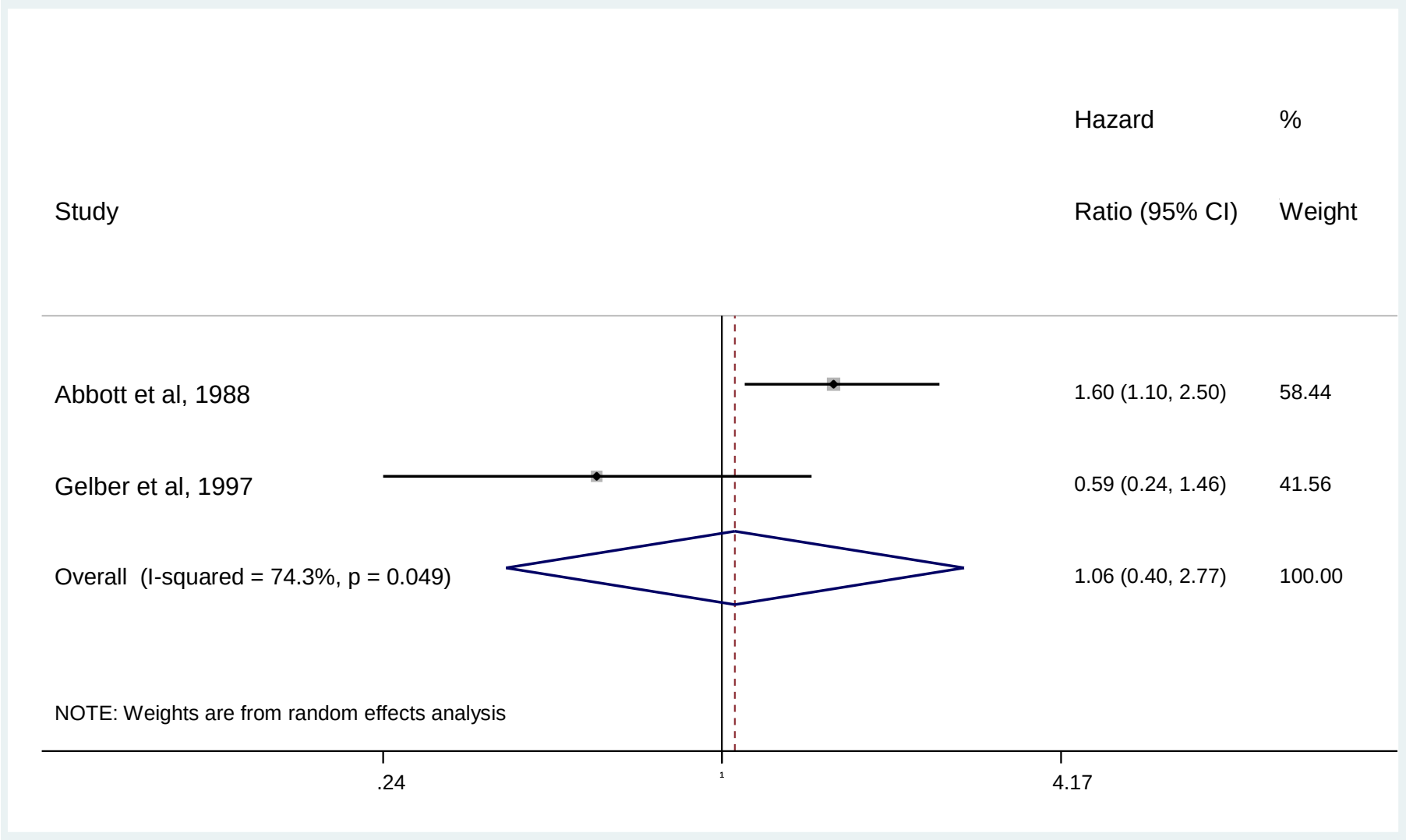


Figure 3.5: Meta-analysis of adjusted findings of studies examining the relationship between gout and incidence of coronary heart disease



Thus, after adjustment for potential confounders, no statistically significant increase in incident coronary heart disease in patients with gout was found, and no significant between study differences were identified.

3.8.2.2.1 Gout and incidence of myocardial infarction

The six studies which examined risk of incident MI in patients with gout also report conflicting findings. An increased incidence of all MI (fatal and non-fatal) was reported in a solely male population by Krishnan et al, 2006, in a mixed population by Kuo et al, 2013, in women but not men by DeVera et al, 2010, but not in either gender by Abbott et al, 1988. (Abbott et al, 1988; De Vera et al, 2010; Krishnan et al, 2006; Kuo et al, 2013) Increased incidence of non-fatal MI was reported in exclusively male populations by two studies, (Choi & Curhan, 2007; Krishnan et al, 2006) in a mixed population by two studies, (De Vera et al, 2010; Seminog & Goldacre, 2013) although one of these found increased risk in women but not men. (De Vera et al, 2010) Two studies examined the incidence of fatal MI, one using an exclusively male population reporting an increased incidence, (Choi & Curhan, 2007) and the other in a mixed gender population where no increased incidence of MI was found after adjustment for other cardiovascular risk factors. (Kuo et al, 2013) The details of these findings are summarised in table 3.8

Table 3.8 Studies investigating gout and the risk of incident MI

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Abbott et al, 1987	Self report	Gout M=53.3/F=58.7 Not gout M=54.6/F=55.3	Gout =83% Not gout = 42% Total = 43%	Excluded if prior HTN and CVD: adjusted for age, BP, total cholesterol, alcohol consumption, BMI, DM	**Men** • Adjusted age only HR 1.4 (0.9-2.3) • Multivariate HR 1.5 (0.9-2.6) **Women**-No significant relationships
Choi & Curhan, 2007	Self-report of physician diagnosis of gout at baseline, incident cases using ACR survey criteria	Gout= 59 Not gout=54	100	Those with and without CHD at baseline analysed separately: Adjusted for age, HTN, HLD, DM, use of aspirin/diuretics, smoking, BMI, physical activity, alcohol intake, FH MI, total energy intake, dietary intake of trans fat/ cholesterol/ protein/ linoleic fatty acid and ratio of polyunsaturated fat to saturated fat	**Non-fatal MI** AHR 1.59 (1.04-2.41)
Devera et al, 2010	ICD-9 codes	Gout M=73.9/F=75 Not gout M=73.3/F=75.0	Gout=59.7% Not gout=59.7% Total 59.7%	Excluded if prior IHD: adjusted for age, HTN, HLD, DM, COPD, Charlson score, monthly prescription drug use – NSAID, diuretic, statin, anticoagulants, aspirin, HRT, steroid.	**All MI** • CHR M= 1.19(1.07-1.32) F= 1.67 (1.45-1.93) • AHR M= 1.11 (0.99-1.23) F= 1.39 (1.20-1.61) **Non- fatal MI** • CHR M= 1.18 (1.05-1.33) F=1.71 (1.44-2.02) • AHR M= 1.11 (0.98-1.25) F= 1.41 (1.19-1.67) **Fatal MI** • CHR M= 1.19 (0.96-1.49) F=1.57 (1.18-2.09) • AHR M= 1.10 (0.88-1.38) F= 1.33 (0.99-1.78)
Krishnan et al, 2006	Self-report physician diagnosed+ documented sustained hyperuricaemia	Total=46 Gout=47 Not gout=46	100	Excluded if previous MI/raised cholesterol/DM or on treatment for or raised BP: adjusted for age, BP, serum cholesterol, creatinine, DM, smoking, FH MI, aspirin, diuretic, alcohol consumption, BMI	**AMI non-fatal** • OR 1.31(1.24-1.38) **All (fatal +non-fatal)** • OR 1.26 (1.14-1.40)

Table 3.8 Studies investigating gout and the risk of incident MI (cont'd)

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Kuo et al, 2013	ICD code – physician recorded	Gout group = 55.4 No gout group = 42.0	Gout=70.3 Not gout=50.4	Age, sex, history of DM, HTN, stroke, ESRD	**All MI** • Age & sex adjusted HR 1.75(1.59-1.94) • AHR= 1.23(1.11-1.36) **Fatal MI** • Age & sex adj HR 1.46 (1.02-2.08) • AHR 0.97 (0.68-1.39) **Non-fatal MI** – Age and sex adj HR 1.78 (1.61-1.98) – AHR=1.26(1.14-1.40)
Seminog & Goldacre, 2013	ICD code-physician recorded	Overall: HES=70.3 ORLS=68.8	Overall: HES=74% ORLS=73%	Age, sex, calendar years in the database, region of residence and deprivation score	**All MI** • AHR HES1.82(1.78-1.85)/ORLS 1.95(1.57-2.40)

ACR = American College of Rheumatology; AHR = adjusted hazard ratio; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHR = crude hazard ratio; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DM = diabetes mellitus; FH MI = family history of myocardial infarction; HES= Hospital Episode Statistics; HLD = Hyperlipidaemia; HR= hazard ratio; HRT = hormone replacement therapy; HTN = hypertension; ICD = International Classification of Diseases; IHD = ischaemic heart disease; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; OR=odds ratio; ORLS= Oxford Record Linkage Study

3.8.2.3 Gout and cardiovascular disease mortality

Eight publications were identified which reported mortality from cardiovascular causes in participants with gout compared to those without (with a combined population of 181,651 gout patients and 3,916,3821 non-gout patients). Six published studies report mortality from any cardiovascular disease as an outcome, (Choi & Curhan, 2007; Kok et al, 2012; Krishnan et al, 2008; Kuo et al, 2010; Stack et al, 2013; Teng et al, 2012) three reported mortality from coronary heart disease, (Choi & Curhan, 2007; Krishnan et al, 2008; Teng et al, 2012) and three reported mortality from MI. (De Vera et al, 2010; Krishnan et al, 2006; Krishnan et al, 2008) The results of these studies will be presented grouped according to the type of cardiovascular disease being investigated in association with mortality in patients with gout.

3.8.2.3.1 Gout and mortality from any cardiovascular disease

The six studies reporting mortality from any cardiovascular cause in participants with gout, compared to those without were all of the cohort design, three from the US, (Choi & Curhan, 2007; Krishnan et al, 2008; Stack et al, 2013) and three from Taiwan. (Kok et al, 2012; Kuo et al, 2010; Teng et al, 2012) Details of the studies reporting mortality from any cardiovascular disease in patients with gout are shown in table 3.9 below.

Table 3.9: Studies examining gout and mortality from any cardiovascular disease

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Choi & Curhan, 2007	Self report of physician diagnosis of gout at baseline, incident cases using ACR survey criteria	Gout= 59 Not gout=54	100	Analysis split into those with CHD at baseline and not – adjusted for age, HTN, HLD, DM, aspirin, diuretic use, smoking, BMI, physical activity, alcohol use, FH MI, dietary constituents	• Age adjusted HR 1.76 (1.47-2.10) • AHR 1.38 (1.15-1.66)
Krishnan et al, 2008	1.Self report physician diagnosed +documented sustained hyperuricaemia 2. use of gout medication in 5y preceding 3.self report of gout without urate level	Gout=52.9 Not gout=52.1	100	Excluded if pre-existing CVD - adjusted for age, BP, serum cholesterol, plasma triglycerides, serum creatinine, glucose, smoking, FH MI, aspirin use, diuretic use, alcohol use, BMI	• CHR 1.30 (1.07-1.58) • AHR 1.21 (0.99-1.49)
Kuo et al, 2010	Physician recorded (record of crystals in fluid or ICD-9 coded as gout) or self report	Gout=52 Not gout=50	Gout=90.4 Not gout=52.4	Excluded those with prior MI or stroke adjusted for features of metabolic syndrome	• CHR 3.59 (1.98-6.47) • AHR 1.97 (1.08-3.59)
Teng et al, 2012	Self report of physician diagnosis + self report of elevated serum urate + self report of dietary advice for gout given	Gout=61.5 Not gout=61.6	Gout=65.7 Not gout=41.5 Model 3 (subgroup with no prior history of vascular disease) =43.3% male	No exclusions in original study – subgroup analysis excludes those with prior vascular disease: adjusted for age, BMI, gender, education, alcohol consumption, smoking, activity, serum cholesterol, fats, HTN, DM	• Men AHR 1.10 (0.82-1.46) • Women AHR 1.51 (1.00-2.30) • All AHR 1.23 (0.97-1.56)
Kok et al, 2012	ICD code-physician recorded	Not stated, all aged over 50	Gout=76.2% Not gout=47.0%	Age, sex, smoking-related diagnosis, alcoholism-related diagnosis, HTN, HLD, Charlson co-morbidity index	• CHR 1.69 (1.65-1.74) • AHR 1.10 (1.07-1.13)
Stack et al, 2013	Self-report of physician diagnosis	Gout = 60 Not gout = 44.3	Gout=68.3% Not gout=47.3	Age, sex, race, coronary disease, congestive heart failure, stroke, diabetes, HTN, physical activity, smoking behaviour, BMI	• CHR 5.25 (3.83-7.19) • AHR 1.58 (1.13-2.19)

ACR= American college of Rheumatologists; AHR=adjusted hazard ratio; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHR=crude hazard ratio; CV= cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HLD= hyperlipidaemia; HTN = hypertension; ICD= International Classification of Diseases; FH MI; family history of myocardial infarction; MI = myocardial infarction

The results of this meta-analysis are shown below in Tables 3.10 and 3.11 presented as the crude results (table 3.10) followed by the adjusted results (table 3.11) and Figures 3.6 and 3.7. The pooled estimate of the HR was 2.01 (95%CI 1.54-2.63) for the crude results, and for the adjusted results was 1.27 (95%CI 1.11-1.46). A statistically significant excess risk of mortality from cardiovascular causes was demonstrated.

Table 3.10: Study effect sizes and weights in meta-analysis of crude results of studies examining the relationship between gout and mortality from any cardiovascular disease

Authors	Hazard Ratio	95% CI	% Weight
Kuo et al, 2010	3.59	1.98-6.47	10.15
Krishnan et al, 2008	1.30	1.07-1.58	18.15
Teng et al, 2012	1.34	1.07-1.69	17.52
Choi & Curhan, 2007	1.76	1.47-2.10	18.43
Kok et al, 2012	1.69	1.65-1.74	20.03
Stack et al, 2014	5.25	3.83-7.19	15.72
D & L Pooled Effect Size	2.01	1.54-2.63	100.00
CI= confidence interval; D&L = DerSimonian & Laird			

I^2= 92.5% which reflects significant heterogeneity, and Cochran's Q test yielded $p<0.01$.

Table 3.11: Study effect sizes and weights in meta-analysis of adjusted results for studies examining the relationship between gout and any cardiovascular disease

Authors	Hazard Ratio	95% CI	% Weight
Kuo et al, 2010	1.97	1.08-3.59	4.53
Krishnan et al, 2008	1.21	0.99-1.49	18.31
Teng et al, 2012	1.23	0.97-1.56	16.06
Choi & Curhan, 2007	1.38	1.15-1.66	19.85
Kok et al, 2012	1.10	1.07-1.13	30.12
Stack et al, 2014	1.58	1.13-2.19	11.12
D & L Pooled Effect Size	1.27	1.11-1.46	100.00
CI= confidence interval; D&L = DerSimonian & Laird			

I^2= 66.9% which reflects significant heterogeneity, and Cochran's Q test yielded $p<0.01$

Figure 3.6: Meta-analysis of crude findings of studies examining the relationship between gout and mortality from any cardiovascular disease

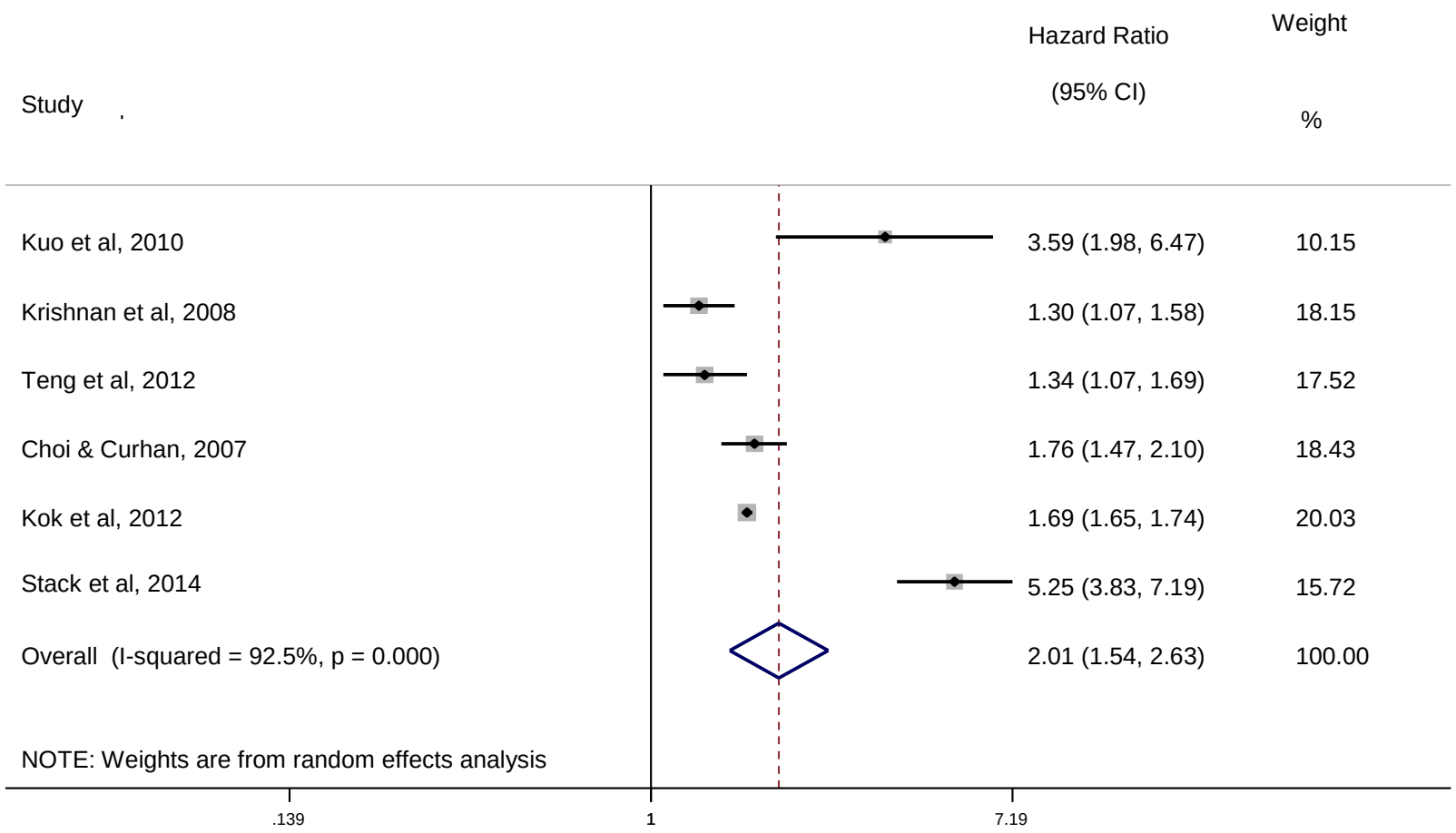
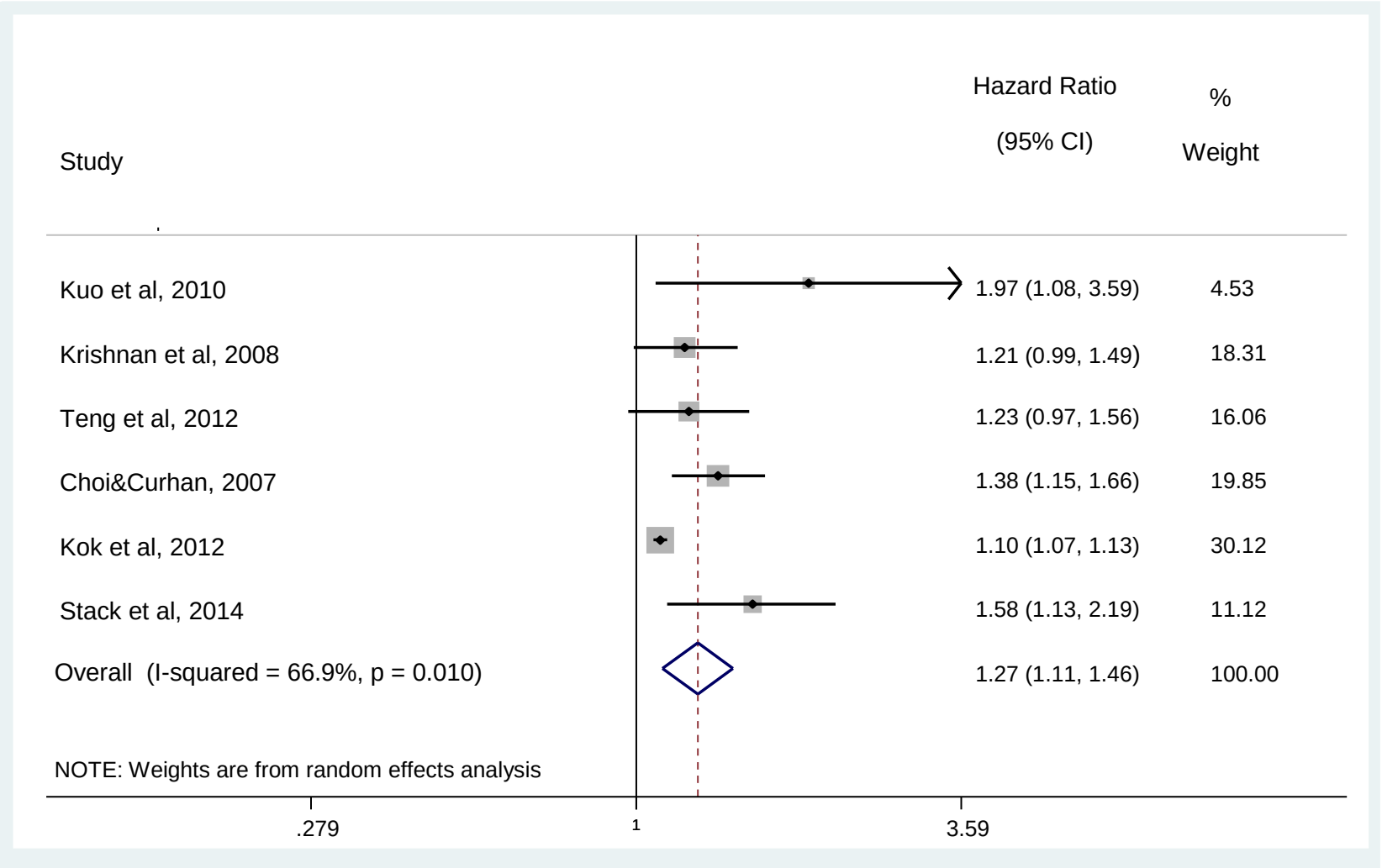


Figure 3.7: Meta-analysis of adjusted findings of studies examining the relationship between gout and mortality from any cardiovascular disease



Thus, even after adjustment for potential confounders, a statistically significant increase in mortality from any cardiovascular disease has been identified in patients with gout, although this may result from between study differences.

3.8.2.3.2 Gout and coronary heart disease mortality

Three cohort studies examine the association between gout and mortality from coronary heart disease, (Choi & Curhan, 2007; Krishnan et al, 2008; Teng et al, 2012) two from the US, (Choi & Curhan, 2007; Krishnan et al, 2008) and one from Taiwan. (Teng et al, 2012) The results of these studies are presented in table 3.12 below

Table 3.12: Studies examining gout and coronary heart disease mortality

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Choi & Curhan, 2007	Self report of physician diagnosis of gout at baseline, incident cases using ACR survey criteria	Gout= 59 Not gout=54	100	Analysis split into those with CHD at baseline and not – adjusted for age, HTN, Serum cholesterol, DM, aspirin, diuretic use, smoking, BMI, physical activity, alcohol consumption, FHMI, Dietary constituents	• CHR 1.95 (1.57-2.44) • AHR 1.55 (1.24-1.93)
Krishnan et al, 2008	1.Self report physician diagnosed +documented sustained hyperuricaemia 2. use of gout medication in 5y preceding 3.self report of gout without urate level	Gout=52.9 Not gout=52.1	100	Excluded if pre-existing CVD - adjusted for age, BP, serum cholesterol, plasma triglycerides, serum creatinine, plasma glucose, smoking, FH, aspirin use, diuretic use, alcohol consumption, BMI	• CHR 1.37 (1.09-1.74) • AHR 1.35 (1.06-1.72)
Teng et al, 2012	Self report of physician diagnosis + self report of elevated serum urate + self report of dietary advice for gout given	Gout=61.5 Not gout=61.6	Gout=65.7 Not gout=41.5 Model 3* =43.3%	No exclusions in original study – subgroup analysis excludes those with prior vascular disease: adjusted for age, BMI, gender, education, alcohol consumption, smoking, activity levels, serum cholesterol, fats, HTN, DM	• Men AHR 1.16 (0.81-1.67) • Women AHR 1.81 (1.07-3.05) • Combined AHR 1.35 (1.00-1.82)
*subgroup with no prior history of vascular disease ACR = American College of Rheumatology; AHR = adjusted hazard ratio; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHR = crude hazard ratio; CVD = cardiovascular disease; DM = diabetes mellitus; FH = family history; FH MI = family history of myocardial infarction; HR= hazard ratio; HTN = hypertension;					

The results of this meta-analysis are shown below in Tables 3.13 and 3.14 presented as the crude results (table 3.13) followed by the adjusted results (table 3.14) and Figures 3.8 and 3.9. The pooled estimate of the HR was 1.60 (95%CI 1.28-2.00) for the crude results, and for the adjusted results was 1.43 (95%CI 1.24-1.65). A statistically significant excess risk of mortality from coronary heart disease was demonstrated.

Table 3.13: Study effect sizes and weights in meta-analysis of crude results of studies examining the relationship between gout and coronary heart disease mortality

Author	Effect Size	95% CI	% Weight
Krishnan et al, 2008	1.37	1.09-1.74	34.89
Teng et al, 2012	1.51	1.13-2.03	28.67
Choi & Curhan, 2007	1.95	1.57-2.44	36.44
D&L Pooled Effect Size	1.60	1.28-2.00	100.00
CI= confidence interval; D&L = DerSimonian & Laird			

I^2 = 59.3% which reflects moderate heterogeneity, but Cochran's Q test yielded p=0.09.

Table 3.14: Study effect sizes and weights in meta-analysis of adjusted results of studies examining gout and coronary heart disease mortality

I^2 = 0.0% and Cochran's Q test yielded p=0.65, suggesting no statistically

Author	Effect Size	95% CI	% Weight
Krishnan et al, 2008	1.35	1.06-1.72	35.13
Teng et al, 2012	1.35	1.00-1.82	22.94
Choi & Curhan, 2007	1.55	1.24-1.93	41.93
D&L Pooled Effect Size	1.43	1.24-1.65	100.00
CI= confidence interval; D&L = DerSimonian & Laird			

significant heterogeneity.

Figure 3.8: Meta-analysis of crude findings of studies examining the relationship between gout and mortality from coronary heart disease

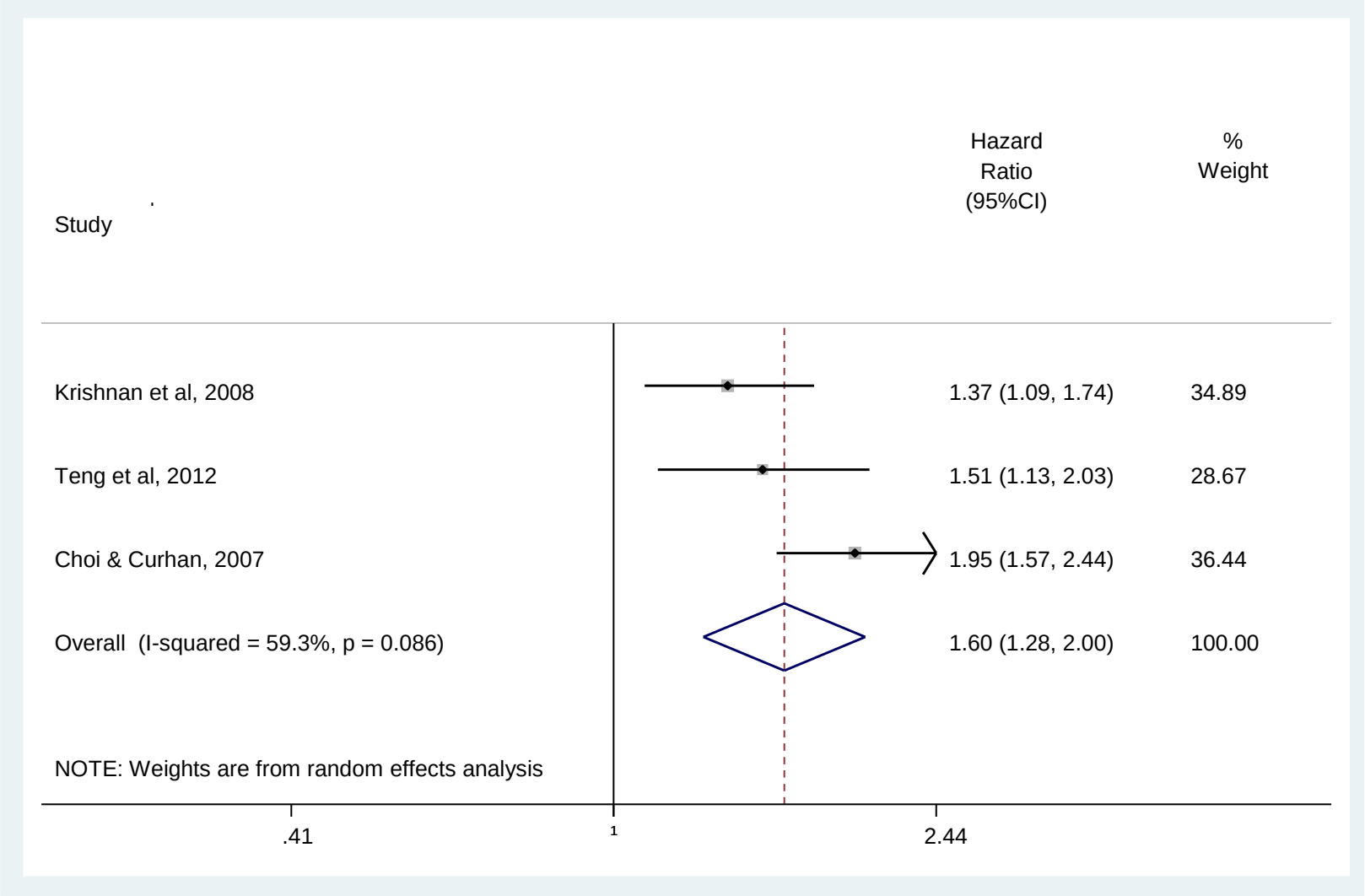
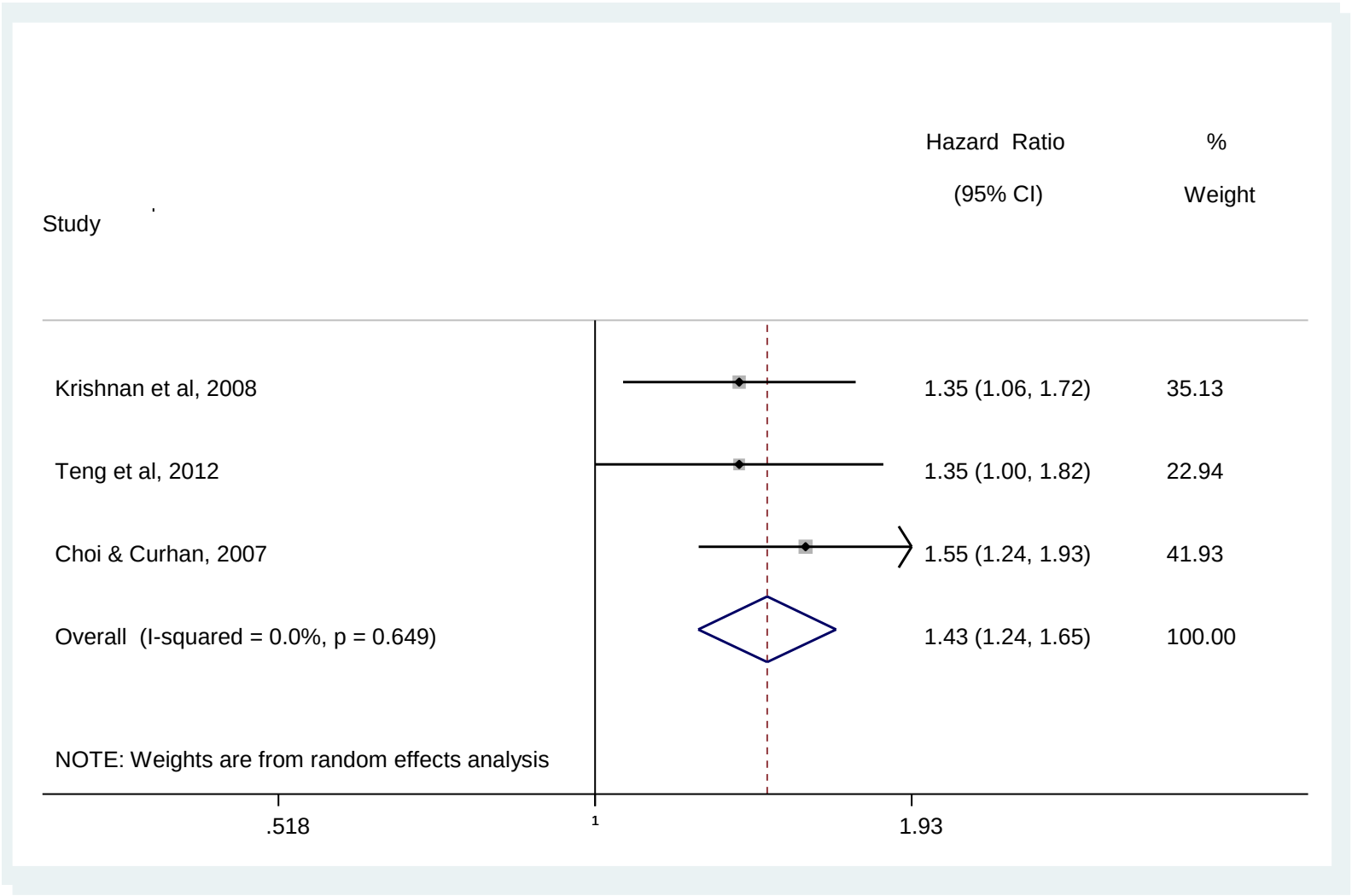


Figure 3.9: Meta-analysis of adjusted findings of studies examining the relationship between gout and mortality from coronary heart disease



Thus, even after adjustment for potential confounders, a statistically significant increase in mortality from coronary heart disease has been identified in patients with gout, which cannot be attributed to between study differences.

3.8.2.3.3 Gout and mortality from myocardial infarction

Two publications were identified which report on the association between gout and mortality from myocardial infarction. (De Vera et al, 2010; Krishnan et al, 2008) Both report the results of cohort studies, one prospective from the US, (Krishnan et al, 2008) and one retrospective from Canada. (De Vera et al, 2010) Krishnan et al, 2008, report an increased risk of fatal acute myocardial infarction in male gout patients in crude analysis, whereas DeVera et al, 2010, report an increased risk of fatal myocardial infarction in female but not male gout patients in crude analysis. (De Vera et al, 2010; Krishnan et al, 2008) However, neither of these studies reported a significant excess risk of mortality from MI in patients with gout, after adjustment for traditional vascular risk factors in either gender. Due to significant differences in the reporting of outcomes, this data is not suitable for meta-analysis and is therefore reported narratively. The details of the studies examining this relationship are shown in table 3.15

Table 3.15 Studies examining the association between gout and mortality from MI

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Devera et al, 2010	ICD-9 codes	Gout M=73.9 F=75 Not gout M=73.3 F=75.0	Gout=59.7% Not gout=59.7% Total 59.7%	Excluded if prior IHD: adjusted for age, HTN, HLD, DM, COPD, charlson score, monthly prescription drug use – NSAID, diuretics, statins, anticoagulants, aspirin, HRT, steroids.	Women • CHR 1.57 (1.18-2.09) • AHR 1.33 (0.99-1.78) Men • CHR 1.19 (0.96-1.49) • AHR 1.10 (0.88-1.38) N.S for gender interaction
Krishnan et al, 2008	1.Self report physician diagnosed +documented sustained hyperuricaemia 2. use of gout medication in 5y preceding 3.self report of gout without urate level	Gout=52.9 Not gout=52.1	100	Excluded if pre-existing CVD - adjusted for age, BP, serum cholesterol, plasma triglycerides, serum creatinine, glucose, smoking, FH, aspirin use, diuretic use, alcohol consumption, BMI	• CHR 1.46 (1.03-2.06) • AHR 1.35 (0.94-1.93)
AHR = adjusted hazard ratio; AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHR = crude hazard ratio; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DM = diabetes mellitus; FH = family history; HLD = Hyperlipidaemia; HR= hazard ratio; HRT = hormone replacement therapy; HTN = hypertension; ICD = International Classification of Diseases; IHD = ischaemic heart disease; MI = myocardial infarction; NS = non-significant; NSAID = non-steroidal anti-inflammatory drug;					

3.8.3 Gout and cerebrovascular disease

Two studies which investigated the relationship between gout and cerebrovascular disease were identified.

Teng et al, 2012, reports no increased risk of mortality from cerebrovascular disease in patients with gout compared to those without in a Taiwanese retrospective cohort study (HR 1.06 [0.63-1.78]). (Teng et al, 2012) In contrast, a retrospective cohort study using two databases of electronic patient records from the UK to investigate the association between gout and incidence of cerebrovascular disease reported an increased risk of all strokes, ischaemic stroke, haemorrhagic stroke and stroke of unspecified aetiology. (Seminog & Goldacre, 2013)

Six other studies report cardiovascular disease including stroke as outcomes. (Choi & Curhan, 2007; Janssens et al, 2003; Kok et al, 2012; Krishnan et al, 2008; Kuo et al, 2010; Stack et al, 2013) Authors were contacted to establish whether any disaggregated outcomes for stroke or cerebrovascular disease could be provided. Two of the authors responded that they were unable to provide this, (Janssens et al, 2003; Kuo et al, 2010) whilst the remainder did not respond. The details of the studies examining this relationship are shown in table 3.16.

Table 3.16 Studies examining the association between gout and cerebrovascular disease

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Mortality from cerebrovascular disease					
Teng et al, 2012	Self report of physician diagnosis + self report of elevated serum urate + self report of dietary advice for gout given	Gout=61.5 Not gout=61.6	Gout=65.7 Not gout=41.5 Model 3 (subgroup with no prior history of vascular disease) =43.3% male	No exclusions in original study – subgroup analysis excludes those with prior vascular disease: adjusted for age, BMI, gender, education, alcohol consumption, smoking, activity levels, serum cholesterol, fats, HTN, DM	• Fatal stroke AHR 1.06 (0.63-1.78) • Men 0.85 (0.43-1.68) • Women 1.45 (0.64-3.29)
Incidence of cerebrovascular disease					
Seminog & Goldacre, 2013	ICD code- physician recorded	Overall: HES=70.3 ORLS=68.8	Overall: HES=74% ORLS=73%	Age, sex, calendar years in the database, region of residence and deprivation score	• All stroke AHR HES 1.71 (1.68-1.75)/ORLS 1.91 (1.70-2.14) • Ischaemic stroke AHR HES 1.68 (1.64-1.73)/ORLS 2.10 (1.61-2.70) • Haemorrhagic stroke AHR HES 1.69 (1.61-1.77)/ORLS 1.95 (1.30-2.81) • Stroke unspecified AHR HES 2.00 (1.95-2.06)/ORLS 1.90 (1.67-2.15)
AHR = adjusted hazard ratio; BMI = body mass index; DM = diabetes mellitus; HES= hospital episode statistics; HTN = hypertension; ICD = International Classification of Diseases; ORLS= oxford record linkage study					

3.8.4 Gout and peripheral vascular disease

Two studies were identified which examined the relationship between gout and peripheral vascular disease (PVD), with one reporting prevalence, and one reporting incidence of PVD in patients with gout compared to those without. (Baker et al, 2007; De Muckadell & Gyntelberg, 1976)

The only study reporting prevalence of PVD in patients with gout was a cross-sectional survey from Denmark. (De Muckadell & Gyntelberg, 1976) They estimated prevalence of PVD in 104 patients with gout and 208 participants without gout and reported an approximately three-fold increase in prevalence of PVD in patients with gout (4.8%) compared to those without (1.4%). However, this difference was not statistically significant.

The only study in which incidence of PVD in patients with gout was investigated was a cohort study from the US, which used participants at increased risk of coronary heart disease initially recruited to a randomised controlled trial investigating the effectiveness of an intervention aimed at reducing their cardiovascular risk. They report an increased risk of incident PVD in patients with gout (n=1485) compared to those without gout (n=11343). However, examining this association was not the purpose of this study and it is likely to have been underpowered to detect any significant difference. (Baker et al, 2007)

The details of these studies are shown in table 3.17 below.

Table 3.17 Studies investigating gout and peripheral vascular disease

Author	Gout definition	Average age	% male	Previous vascular disease or risk factor information	Outcomes
Prevalence of PVD					
Schaffalitzky de Muckadell & Gyntelberg, 1976	Patient recall of physician diagnosed gout	Not described – all between 40 and 59	100	Pt recall data	% prevalence of intermittent claudication • Gout = 4.8% • Non-gout = 1.4% • Difference N.S
Incidence of PVD					
Baker et al, 2007	Self report	46	100	Excluded if prior MI, angina, DM, body weight>150% desirable, HLD, HTN: adj for age, FH cardiovascular disease, DM, HLD, Smoking, HTN, BMI	• OR 1.33 (1.07-1.66)
BMI=body mass index; DM=diabetes mellitus; FH= family history; HLD= hyperlipidaemia; HTN= hypertension; MI = myocardial infarction; NS = non-significant; OR = odds ratio					

3.9 Assessment of heterogeneity

This section will examine possible explanations for the heterogeneity of the included studies.

Due to the wide range of outcomes reported in the included studies, and the fact that some studies report more than one outcome measure, for the purposes of this analysis, publications are split into those reporting any significant increased risk of vascular disease in patients with gout, and those that do not.

The first section will assess heterogeneity in the context having achieved or not achieved the quality criteria set out earlier in this chapter.

The second section will assess heterogeneity in the context of other study criteria, such as study population size, gender distribution and geographical location.

3.9.1 Assessment of heterogeneity and quality assessment criteria

Fisher's exact test was used to test differences in having met (or not met) the individual quality criteria between those studies which showed any increased risk of vascular disease in gout patients, and those that did not find any such association. The small number of articles meant that non-parametric testing was required and so the Fisher's Exact Test, rather than the chi squared test was applied. (Fisher, 1922) Table 3.18 shows the results of this statistical testing. Taking a p value of less than 0.05 to determine statistical significance, Table 3.18 can be clearly seen to show no statistically significant differences between

achievement of quality criteria between those studies which demonstrate an increased risk of vascular disease in gout, and those that do not.

Table 3.18: Table presenting the numbers of studies reporting an increased risk of vascular disease in gout (significant) compared with those that did not, and which met/did not meet the set quality criteria, with the statistical significance of this difference

		Quality Criteria										
		1	2	3	4	5	6	7	8	9	10	11
Significant	Met	8	13	9	9	12	10	13	12	5	13	13
	Unmet	5	0	4	4	1	3	0	1	8	0	0
Non-significant	Met	3	4	3	4	2	4	4	4	4	4	4
	Unmet	1	0	1	0	2	0	0	0	0	0	0
2 Tailed Significance level using Fisher's Exact Test		1.0		1.0	0.50	0.20	0.50		1.0	0.07		

3.9.2 Assessment of heterogeneity and study characteristics

In this section, the heterogeneity of the results of the included studies which report an association between gout and risk of vascular disease compared with those that do not will be discussed with reference to certain study characteristics. These were;

1) Geographical location of the study: the two groups were compared according to whether the studies were conducted in the United States and Canada or elsewhere.
2) Size of the total study population: studies were divided into those that had >10,000 participants and those that did not.
3) Gender distribution of study population: studies were divided into those with all male participants and those with some female participants.

Fisher's exact test (for reasons explained in section 3.6 and 3.9.1) was used to test differences in presence or absence of these study characteristics described between those studies which showed any increased risk of vascular disease in gout patients, and those that did not find any such association. Table 3.19 shows the results of this statistical testing. Taking a p value of less than 0.05 to determine statistical significance, Table 3.19 can be clearly seen to show no statistically significant differences in presence or absence of these study characteristics between those studies which demonstrate an increased risk of vascular disease in gout, and those that do not.

Table 3.19: Table presenting the numbers of studies reporting an increased risk of vascular disease in gout (significant) compared with those that did not, and which met/did not certain population characteristics, with the statistical significance of this difference

		Study Characteristics		
		Study based in the US or Canada	Study population >10,000	All male population
Significant	Met	7	9	5
	Unmet	6	4	8
Non-significant	Met	2	2	1
	Unmet	2	2	3
2 Tailed Significance level using Fisher's Exact Test		1.00	1.00	0.56

3.10 Assessment of publication bias

Evidence of publication bias was assessed using funnel plots and Begg's and Egger's tests. These are presented below, however the results should be interpreted with caution since the small number of papers included in each analysis significantly limits the power of Begg's or Egger's test.

Mortality: Any cardiovascular disease

Figure 3.10 Funnel plot of publications examining the relationship between gout and mortality from any cardiovascular disease (adjusted results)

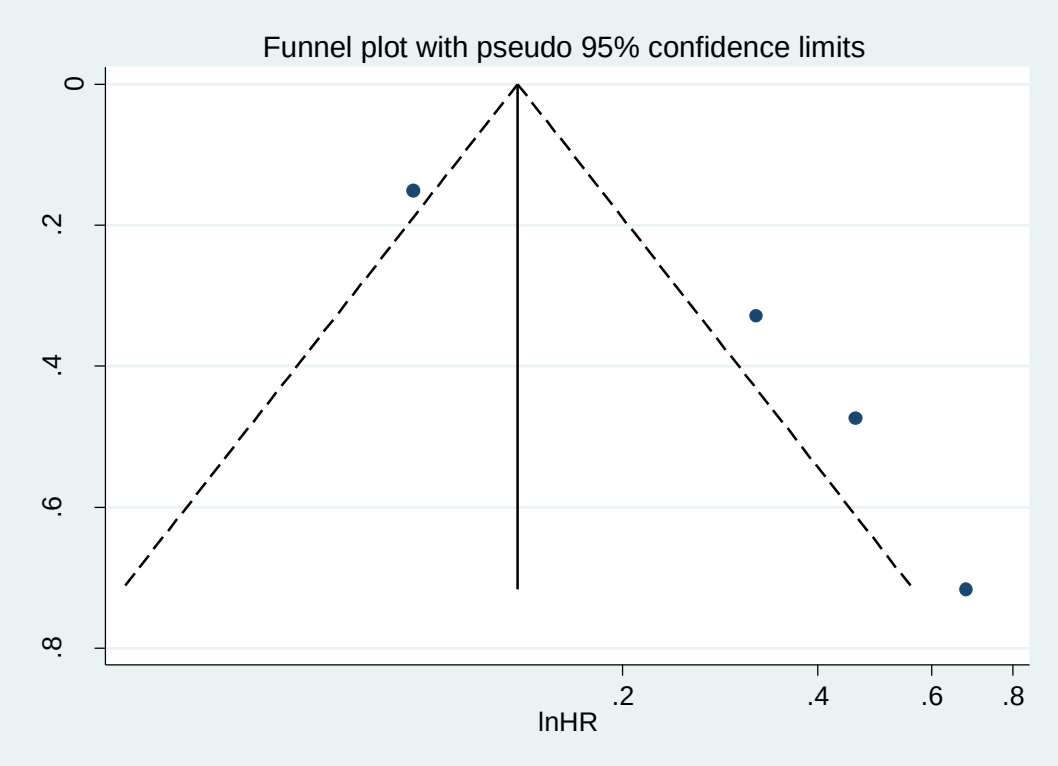


Table 3.20 Results of Begg's and Egger's tests in assessing publication bias in studies examining the relationship between gout and mortality from any cardiovascular disease

	Test value	p for significance
Begg's test	0.61	0.66
Egger's test	1.13	0.26

There is evidence of some publication bias in the relationship between gout and any cardiovascular mortality, seen in the funnel plot where there is an obviously skewed distribution of markers, but the statistical tests applied do not show any evidence of publication bias. This discrepancy demonstrates the low power of Begg's and Egger's tests to detect publication bias where the number of included studies is small.

Mortality: Coronary heart disease

Figure 3.11 Funnel plot of publications examining the relationship between gout and mortality from coronary heart disease (adjusted results)

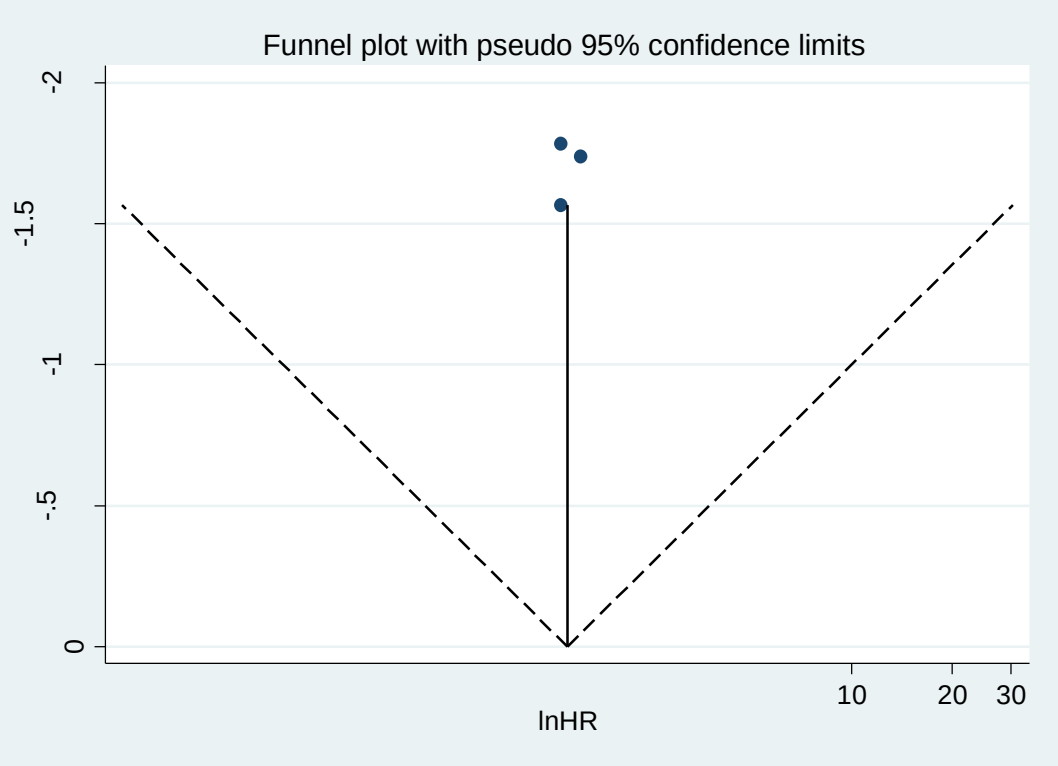


Table 3.21 Results of Begg's and Egger's tests in assessing publication bias in studies examining the relationship between gout and mortality from coronary heart disease

	Test value	p for significance
Begg's test	-0.52	0.602
Egger's test	-0.27	0.723

There is no evidence of publication bias shown in either the funnel plot where the markers are all clustered around the null value, or the statistical tests applied which are both non-significant.

Incidence: Coronary heart disease

Figure 3.12 Funnel plot of publications examining the relationship between gout and incidence of coronary heart disease (adjusted results)

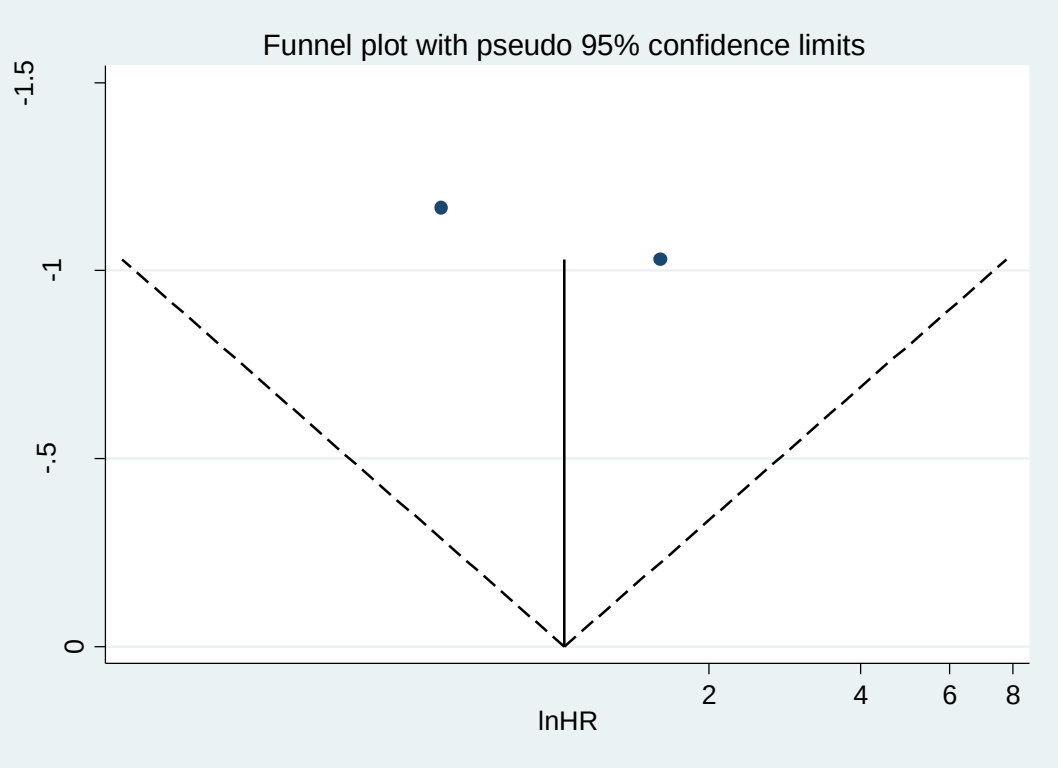


Table 3.22 Results of Begg's and Egger's tests in assessing publication bias in studies examining the relationship between gout and incidence of coronary heart disease

	Test value	p for significance
Begg's test	1.00	0.317
Egger's test	7.23	not given

There is no evidence of publication bias, since distribution across the funnel plot is symmetrical, and Begg's test is non-significant, although there are only two studies included.

3.11 Discussion

This section will discuss both the results of the studies identified by this review, and their design and methodological quality.

3.11.1 Discussion of the relationship between gout and vascular disease

The results of this review demonstrate an increased risk of mortality from any cardiovascular cause and coronary heart disease, but not MI, whereas these relationships are reversed when incidence of disease is measured, with increased incidence of MI reported, but not increased incidence of any cardiovascular disease or coronary heart disease.

These results are consistent with the only previous systematic review of 4 studies, which concluded that gout is an independent risk factor for cardiovascular mortality. (Lottmann et al, 2012) 3 of the studies included in that review were included in this meta-analysis, (Choi & Curhan, 2007; Krishnan et al, 2008; Kuo et al, 2010) however one was excluded, (Cohen et al, 2008) since the study population consisted of renal dialysis and transplantation patients, and was not felt to be broadly representative of the wider gout population. Five additional newer studies were included in this review. (Kok et al, 2012; Kuo et al, 2013; Seminog & Goldacre, 2013; Stack et al, 2013; Teng et al, 2012)

There are a number of possible explanations for the disparity in association between gout and incidence and mortality from different types of vascular disease.

In the case of an association between gout and risk of any cardiovascular and CHD mortality, but not MI mortality the most obvious reason is ascertainment bias,

where deaths are attributed to a cardiovascular or CHD cause when in fact this is not the true cause of death, This is less likely to be the case with MI where a reliable combination of electrocardiogram findings and biochemical test results are required to make the diagnosis. Linked to this is the concept of spectrum bias, whereby any cardiovascular disease and CHD cover a broader range of conditions, and in fact in some of the studies include cerebrovascular disease, (Choi & Curhan, 2007; Janssens et al, 2003; Kok et al, 2012; Krishnan et al, 2008; Kuo et al, 2010; Stack et al, 2013) resulting in the more frequent recording of codes relating to any cardiovascular disease and CHD than MI. Thus comparatively less MI's are likely to be detected in both gout and non-gout groups in studies using retrospective record review, and even fewer fatal MI's, thus the studies may not be large enough to detect sufficient events to detect an association.

It may genuinely be the case that there is not an increased mortality from MI associated with gout, and that gout only increases risk of non-fatal MI. Alternatively this finding may represent the effect of surveillance bias, with screening for and management of vascular risk factors in patients with gout, or lifestyle advice given following diagnosis of gout, preventing otherwise fatal MI. However, there is evidence to suggest that only the minority of patients with gout have screening for cardiovascular risk factors within a month following diagnosis. (Roddy et al, 2010) It is more likely to represent misclassification with poor identification and/or coding of MI compared with other forms of vascular disease, perhaps using more general cardiovascular or CHD codes and thus attributing the death to these causes.

Competing risks must also be considered in associations with mortality, whereby when a study is interested in cause-specific mortality and there is a significant and competing risk, such as mortality from another cause, for example end-stage renal disease (ESRD) or cancer, then patients who die from the competing risk can no longer remain at risk of mortality from the cause of interest. Thus, the estimate of risk of mortality from the cause of interest will be attenuated by patients who can no longer remain "at risk" of mortality from MI since they have already died of something else. Therefore, it is possible that gout is associated with an increased risk of non-fatal MI, but then patients die of an alternative cause such as heart failure, recorded as CHD or CVD, or a different system disorder such as ESRD.

The lack of association with incidence of cardiovascular disease and CHD may be the result of only two studies investigating this particular association. Perhaps future studies examining incidence of disease will alter this finding, or simply confirm the lack of association. Assuming, however, that these findings are not the result of bias, inadequate study size to detect events, or neglect of incidence as an outcome, there may be other factors influencing these relationships resulting in the differences between associations of incidence and mortality from cardiovascular disease, CHD and MI.

The increased mortality from, but not incidence of CVD and CHD, and increased incidence of, but not mortality from MI may be explained by relative difference in risk factors for the onset of different manifestations of cardiovascular disease. There is evidence to suggest that the risk factors for stable angina are different from those for unheralded MI or acute coronary syndrome (ACS) at first presentation. (Canoui-Poitrine et al, 2009; Dunder et al, 2004) Rheumatoid

arthritis patients have been reported to be less likely to report symptoms of angina, but more likely to experience unrecognised MI and sudden death. (Maradit-Kremers et al, 2005) This may be explained by the evidence to suggest circulating plasma levels of proinflammatory cytokines differ in stable and unstable angina, with raised IL-1β levels significantly higher in those with unstable than stable angina, or controls. (Simon et al, 2000) Inflammation has been implicated in all phases of athero-thrombosis, including rupture of atherosclerotic plaques responsible for acute cardiac and cerebrovascular circulations. Interleukins 1 and 6 are particularly implicated, with evidence that IL-1 can induce a procoagulant state, as well as monocyte and leucocyte adhesion in human vascular endothelial cells, and increased levels of IL-1β in atherosclerotic compared with normal coronary arteries. (Ridker et al, 2011) IL-6 has been shown to be an independent risk factor for cardiovascular disease mortality, (Lee et al, 2012; Su et al, 2013) and a strong independent relationship between circulating IL-6 levels and endothelial activation in patients with rheumatoid arthritis. (Dessein et al, 2013)

There is evidence that the NALP3 inflammasome, triggered to produce active IL-1 by the presence of MSU crystals, is also activated by cholesterol crystals and LDL cholesterol. (Duewell et al, 2010) There is also evidence that management of disease burden in rheumatoid arthritis has been shown to reduce dyslipidaemia. (Steiner & Urowitz, 2009) Although there is a paucity of evidence examining how the management of gout affects long-term outcomes, it would seem that in a condition known to caused increased circulating levels of IL-1 and IL-6 predisposing to atherosclerosis, and where co-morbid vascular risk factors such as dyslipidaemias are common, it would seem that further investigation of ways to reduce these risks is warranted. Of particular interest is the evidence that only

40% of patients with gout receive urate lowering therapy (ULT), (Annemans et al, 2008; Kuo et al, 2014) and that persistence with such ULT is poor, (De Vera et al, 2014; Kuo et al, 2014) which when considered alongside the presence of sub-clinical inflammation even in the asymptomatic intercritical period, suggests the majority of gout patients remain at increased risk.

Two of the studies included in this review were cohort studies which followed randomised controlled trials, where patients from all arms of the trial who did not develop the original outcome of interest within the trial follow-up were then observed as part of a cohort study. One of the two studies examining incidence of CVD in patients with gout was one of these cohort studies originating from a trial population. Recruitment to trials can often have very specific inclusion criteria, often resulting in a very niche population remaining to be included in any subsequent cohort study, potentially influencing the strength of the association, however as a large prospective cohort study, where the inclusion criteria applied to all participants with and without gout, it was felt appropriate to include this study.

Two studies examine the relationship between gout and cerebrovascular disease, one reporting no increased risk of fatal stroke in patients with gout after adjustment for vascular risk factors, (Teng et al, 2012) but the other reporting increased incidence of all types of stroke in patient with gout. (Seminog & Goldacre, 2013) These findings are not in complete agreement with a previous systematic review which linked hyperuricaemia with increased risk of both stroke incidence and mortality. (Kim et al, 2009) This may reflect the inclusion of cerebrovascular outcomes as part of cardiovascular disease outcomes, (Choi & Curhan, 2007;

Janssens et al, 2003; Kok et al, 2012; Krishnan et al, 2008; Kuo et al, 2010; Stack et al, 2013) and a relative paucity of literature on this particular relationship.

Literature examining the relationship between gout and peripheral vascular disease is also limited. Although the one published study reporting on this association reports an increased risk of incident peripheral vascular disease in patients with gout, compared to those without gout, OR 1.33 95%CI[1.07-1.66], (Baker et al, 2007) this was not the purpose of this study and it is likely to have been underpowered to detect any difference. This in keeping with literature linking hyperuricaemia with peripheral vascular disease, (Langlois et al, 2003; Shankar et al, 2008; Tseng, 2004; Vigna et al, 1992) which is unsurprising given the many common risk factors such as hypertension, diabetes, metabolic syndrome, chronic kidney disease (CKD) and smoking, (Shammas, 2007) that the two conditions share.

3.12 Strengths and Limitations of the Review

The strengths of our review include our inclusion criteria, with initially only case-control study designs excluded, and finally only large cohort studies included. This eliminated the recall bias associated with the case-control study design. Participants were all required to be disease free at baseline and thus, cases of vascular diseases identified were truly incident. Whilst some cohorts originated in controlled trials, participants who continued in these observational studies were observed for up to 17 years following the end of the trial perhaps compensating for more stringent enrolment criteria in the original trials.

Rigorous data extraction was also a strength of this review. All papers were independently assessed for inclusion or exclusion by two reviewers, with a third reviewer identified in the case of disagreement. Authors were contacted for additional information where necessary. A validated tool appropriate for cohort studies, the Newcastle-Ottawa Scale, was used to quality assess papers, with the addition of criteria considered to be important to this particular study. These additions quality assessed areas of the study papers not included in the NOS tool, appropriateness of statistical methods, and the separation of asymptomatic hyperuricaemia from clinical gout, since this distinction is important in accurately estimating any association between gout and vascular disease.

Crude and multivariate data were pooled separately and examined for potential sources of heterogeneity (geographical location of study, year of publication, gender distribution), and studies which did and did not report associations were compared by met and unmet quality assessment criteria to establish statistically significant trends. Where studies were considered too heterogeneous for meta-analysis data was described narratively. Finally no evidence of publication bias was found in our review.

Limitations of our review include the small number of papers available for inclusion in the review, particularly about the association between gout and cerebrovascular and peripheral vascular disease (cardiovascular n=14; cerebrovascular n=2; peripheral vascular disease n=1). Despite a thorough and comprehensive search strategy the possibility remains that some relevant articles may not have been identified. Similarly, studies with negative findings are less likely to be published, and publication bias may be introduced, and this was difficult to assess for the

majority of the outcomes due to the small number of papers identified. The paucity of evidence investigating the association between cerebrovascular and peripheral vascular disease in particular limits the reliability with which this review can conclude that an association with gout is indeed present, although it may be that some publications reporting investigation of this relationship were excluded since it was not possible to translate them into English language.

There was some degree of heterogeneity in the definitions of gout used in the studies, from self-report to those including medical record review. Clearly the reliability of case definition of gout will affect the magnitude of the association, and thus had more stringent definitions been used throughout then a different pattern of association may have been seen. Similarly, the potential confounders adjusted for in the multivariate analyses also differed between studies. If some studies fail to adjust for important cofounders and therefore report a spurious association this will be reflected in the review. Despite the size of many of the studies, serum urate levels and disease severity were not included in many of the studies which may have influenced the associations observed. As previously discussed, misclassification (ascertainment) bias must be considered in both the recording of gout and the vascular outcomes of interest, and competing risks could not be accounted for in the estimation of association with mortality from vascular causes.

3.13 Summary

This review finds that gout is an independent risk factor for mortality from all cardiovascular disease and coronary heart disease but not myocardial infarction, and is an independent risk factor for incidence of myocardial infarction but not all cardiovascular disease or coronary heart disease. It was noted that incidence of

cardiovascular disease was neglected as an outcome in current literature in comparison with mortality.

The literature is inadequate to determine whether any association exists between gout and cerebrovascular or peripheral vascular disease, and incidence of cardiovascular disease and further research on these particular relationships is required.

Chapter 4: Retrospective Cohort Study Methodology

4.1 Overview

This chapter will describe the choice of methodology used to investigate the association between gout and vascular disease, including study design, study population, potential sources of bias and statistical analysis.

4.2 Background

The evidence reviewed in chapters two and three has identified gaps in the existing literature examining the relationship between gout and vascular disease, particularly the relationship between gout and the incidence of all types of vascular disease (cardiovascular, peripheral vascular and cerebrovascular). Appropriate examination of these potential associations will require a study design which will allow the determination of the incidence of vascular diseases in patients with and without exposure to gout, taking into account other potential confounding exposures (e.g. smoking or hypertension) which may also influence the risk of vascular disease. Two study designs lend themselves to an investigation of this kind. These are the cohort study design and the case-control study design.

4.3 Choice of study design

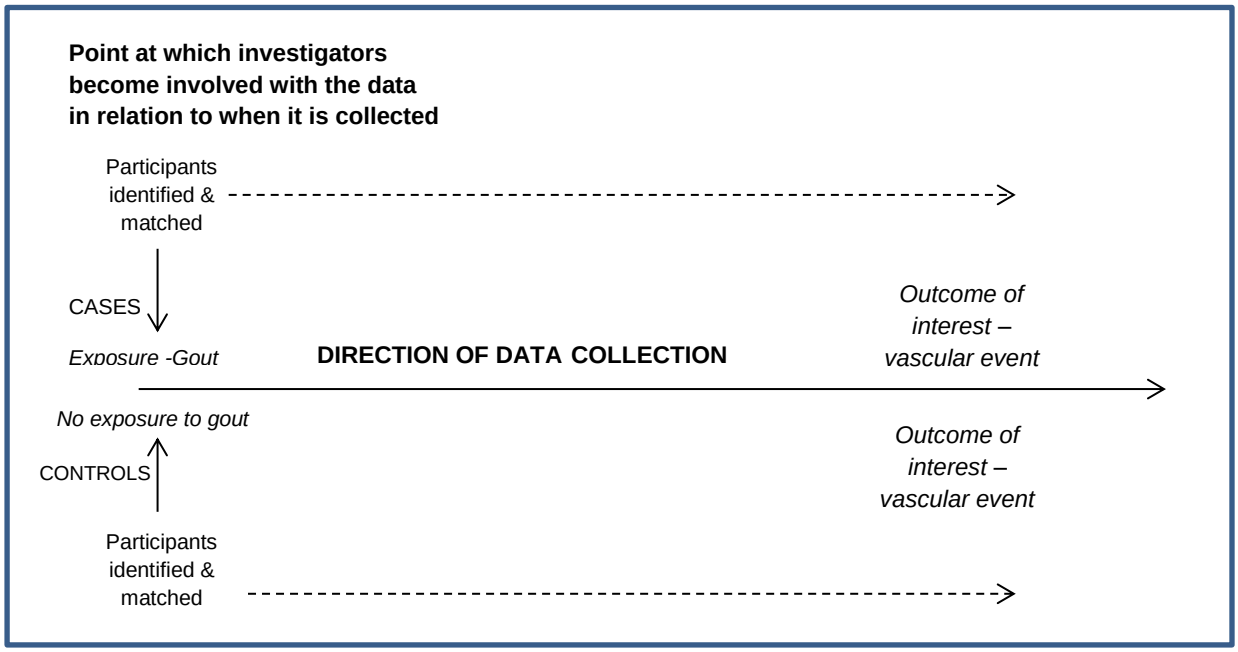
A cohort study design was chosen as the primary aim of the study was to investigate the association between gout and incident vascular disease in a primary care population, taking account of other vascular risk factors, in order to better inform clinicians and patients in managing both their gout and its comorbidity. A cohort study design compares groups of people, based upon an

exposure or disease of interest (e.g. gout), and follows them to determine whether that exposure makes that group more or less likely to develop an outcome of interest (e.g. first vascular event). Several of the studies identified in chapter 3 have utilised this design to investigate associations between gout and vascular disease, including the Framingham Study, (Abbott et al, 1988) the Multiple Risk Factor Intervention (MR-FIT) Study, (Krishnan et al, 2008) and the Health Professionals Follow-up Study. (Choi & Curhan, 2007) Cohort studies can be described as either prospective or retrospective, and the relative merits of each of these will be discussed below.

4.3.1 Prospective Cohort Studies

Prospective cohort studies are conceived, designed and patients enrolled prior to them having developed the outcome of interest. A pictoral representation of the prospective cohort study design is shown in Figure 4.1.

Figure 4.1: Pictoral representation of the prospective cohort study design

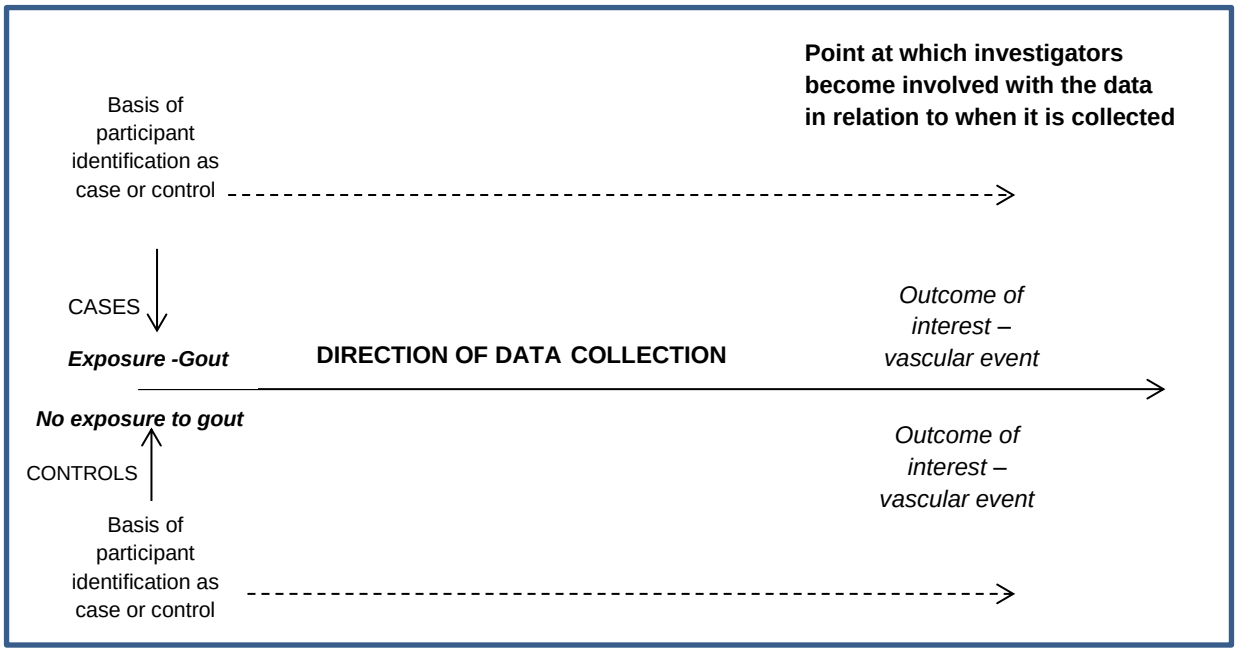


4.3.2 Retrospective Cohort Studies

Retrospective studies are conceived and designed after some of the outcomes of interest have already developed. For this reason, the data used has usually been collected for another purpose, for example, primary care healthcare records, or death registries.

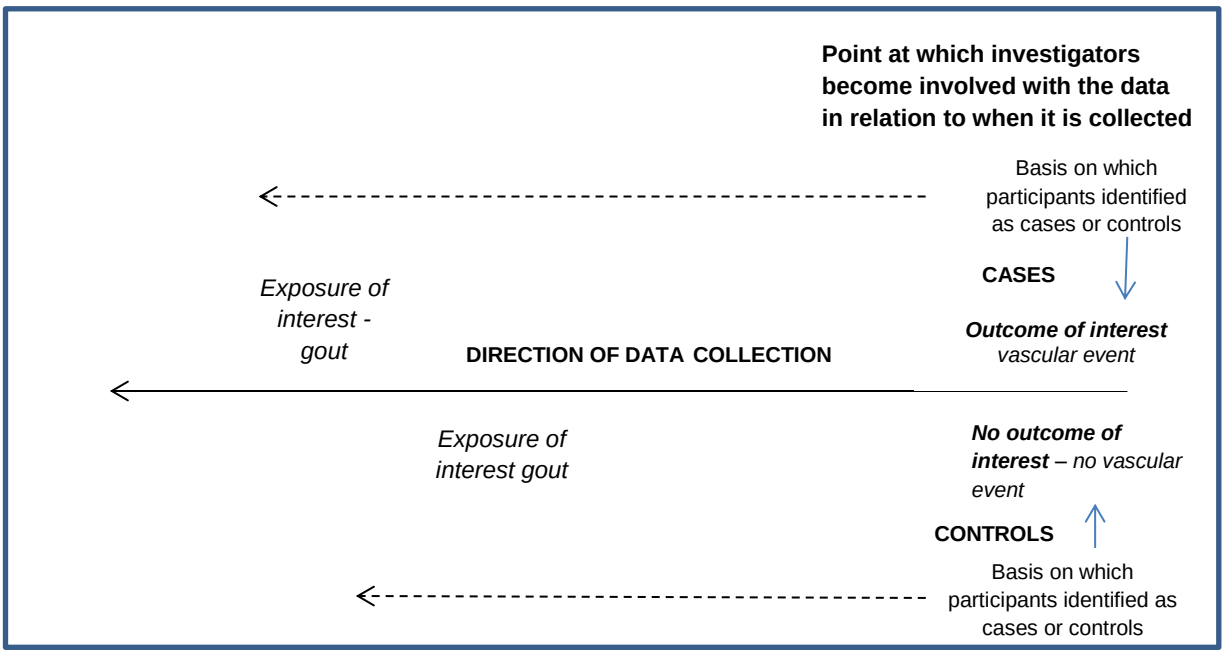
The retrospective cohort study design is represented in Figure 4.2 below

Figure 4.2: Pictoral representation of the retrospective cohort study design



The retrospective cohort study is often confused with the case-control study since both use patients in whom outcomes of interest may already have developed, however they can be distinguished by the way in which “cases” and “controls” are matched. Figure 4.3 gives a pictoral representation of the case-control study design.

Figure 4.3: Pictoral representation of the case-control study design



Figures 4.2 and 4.3 illustrate the differences between the retrospective cohort study design and the case-control design. The retrospective cohort study, despite the data and outcomes already having been recorded, investigates associations between exposures and outcomes by matching cases and controls on their exposure status (gout or no-gout). In a case-control study, participants are matched on whether or not they have the outcome of interest (vascular disease) and their records then examined for evidence of exposures of interest (gout).

4.3.3 Relative advantages and disadvantages

The advantages and disadvantages are shown for comparison on Table 4.1 below.

Table 4.1 Advantages and disadvantages of cohort and case-control study designs

	Prospective cohort study	Retrospective cohort study	Case-control study
Advantages	• Can be designed to answer specific questions • Can collect data at pre-determined points in time • Can validate exposures and diseases in real time • Loss to follow up can be minimised since participants can be contacted	• Less time consuming • Less expensive • Can utilise pre-existing sources of data e.g. electronic medical records • Can be used to examine rare exposures • Can examine multiple outcomes for a particular exposure	• Quicker • Cheaper • No loss to follow-up • Can utilise existing records, e.g. electronic medical records • Can be used to examine rare outcomes • Multiple risk factors can be investigated simultaneously
Disadvantages	• Often long follow-up required • Expensive • Labour intensive	• Data cannot be pre-specified as usually collected for alternative purpose • May be incomplete data on variables of interest, introducing information or recall bias • Loss to follow up cannot be influenced	• Risk of recall bias since patients who have the condition of interest more clearly recall particular exposures than those who do not • Accuracy of diagnoses or exposures cannot be validated since data is pre-recorded • Not suitable for investigation of rates of disease in exposed and unexposed individuals

4.3.4 Advantages specific to the association of interest

The main advantage of using a cohort study design to investigate the association between gout and vascular disease is the ability to calculate rates of vascular disease in exposed (patients with gout) compared to unexposed (patients without gout) patients over time. This would generate a measure of risk that is both clinically meaningful, and easy for patients to understand and discuss when making health choices, since it is easy for patients to understand the risk of an outcome (e.g. vascular disease) in an exposed group (e.g. patients with gout) compared to the risk in an unexposed group, for example that a hazard ratio of 1.2 suggests that those with gout have a 20% greater chance of developing vascular disease than those without gout given similar risk factors and follow-up time.

This study design can also investigate multiple risk factors associated with an outcome, and thus other traditional vascular risk factors such as hypertension and smoking can also be considered.

The cohort design would also allow the choice of either a prospective design, or a retrospective design using existing records, such as a database of primary care electronic health records (EHR).

A retrospective study design was chosen for this investigation because considerable follow-up time may be required to detect incident vascular disease, making a prospective study potentially very lengthy and costly. Further investigating this relationship in a primary care population could be achieved using large existing databases of EHR, which routinely collect data on the majority of

vascular risk factors of interest and lend themselves to the retrospective cohort design.

4.4 Study population

Having chosen the retrospective study design, this section will describe the selection of the study population.

4.4.1 Use of electronic medical records for research

The use of data from routinely collected from EHR has been found to be a cost-effective way to undertake epidemiological studies of large patient populations. (Jordan et al, 2006) Furthermore, in excess of 98% of the UK population are registered with a GP, (Agarwal & Crooks, 2008) making the use of electronic EHR a convenient way to sample the general population. Important insights into the epidemiology of diseases presenting in primary care can be gained, as well as information about consultation behaviour of patients, and management of conditions offered by GPs.

All consultations and healthcare transactions are recorded within this record, from a diagnostic Read code labelling each encounter with the main reason for consultation, to results of investigations, prescription and referral data. Furthermore, in addition to the consultations initiated by the patient, additional data is collected routinely through primary care, such as blood pressure readings, weight monitoring, smoking status and levels of alcohol consumption, often on an annual basis, making some of the information which may have been collected in a

prospective cohort study available to those using EHR to undertake retrospective studies.

Comparable data from secondary care in the UK is less accessible as paper based records are largely used in hospital settings, rather than electronic ones. This is in contrast to the USA, where the privatised nature of their healthcare system allows for the interrogation of databases of administrative claims for episodes of care which can be used to obtain similar data.

In the UK, there are three predominant databases used for epidemiological research using primary care data. These are the Clinical Practice Research Datalink (CPRD) (formerly known as the General Practice Research Database (GPRD)), The Health Improvement Network (THIN), and QResearch. QResearch has not been used to investigate the epidemiology of gout, however both CPRD and THIN have been used for both case-control and cohort studies on these subjects. The existing studies are shown in table 4.2 below.

Table 4.2 Existing cohort studies relating to gout in primary care databases

Author	Year of Publication	Number of Participants	Subject
CPRD			
(Mikuls et al, 2005a)	2005	63,105	Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia
(Mikuls et al, 2005b)	2005	1,716,276	Gout epidemiology
(Kuo et al, 2014)	2014	4,634,974	Trends in the epidemiology of gout and patterns of use of ULT
THIN			
(Soriano et al, 2011)	2011	1,775,505	Epidemiology of gout in the UK
(Rothenbacher et al, 2011)	2011	23,857	Frequency and risk factors of gout flares in a large population-based cohort of incident gout
CPRD=clinical practice research datalink; THIN=the health improvement network; UK=United Kingdom; ULT=urate lowering therapy			

4.4.2 Matching

In any study comparing groups, similarities and differences between groups must be considered. Matching aims to ensure selection of a comparator group that is similar to another group with respect to the distribution of one or more confounding factors, and is one way reduce the risk of spurious findings resulting from these differences. (Bland & Altman, 1994)

In a cohort study such as this, matching is done based upon exposure status (gout vs non-gout), to ensure that within the study sample, exposed and unexposed patient cohorts are similar in ways which may affect the direction or magnitude of any association found. For example, if samples were not similarly distributed across age ranges, then as vascular disease becomes more likely with increasing

age, any association identified may simply reflect one cohort being older than the other, and not excess risk due to gout.

Matched sampling leads to a balanced number of exposed and unexposed subjects across the selected matching variables. This balance can reduce the variance in the parameters of interest, which improves statistical efficiency. Using age as an example again, when comparing groups by age band, unmatched cohorts may result in a Type II error, since an effect may not be detected if the number of cases or controls in each age group are too small, rather than because there is in fact no association. Matching ensures that there is at least one or more matched controls present in the same age band as the case, removing the resulting risk of spurious acceptance of the null-hypothesis. This may also increase the efficiency of a study, and control for factors not easily measured, by optimising the amount of information gathered from each subject rather than increasing the number of subjects. (Rothman & Greenland, 1998)

There are disadvantages to matching. Firstly, matching on causal variables may introduce selection bias, which is a bias resulting from a systematic difference between groups being compared due to non-random or flawed selection of participants. (Rothman & Greenland, 1998) Secondly, the contribution of the matching variable to the association of interest cannot be examined because matching creates a sample of controls that is not representative of the population as a whole, since the frequency of exposure in the control sample will be shifted towards that of the cases. (Rothman & Greenland, 1998)

4.4.2.1 Choice of matching criteria

In this study cases and controls were matched on the basis of age, gender and registered general practice. These criteria for matching were chosen since both gout and vascular disease become more common with age, have different gender biases, and may be influenced by socio-economic factors. Furthermore, although these factors are likely to influence the occurrence of vascular disease in patients with gout, they are not causal, and therefore matching on these factors removes their ability to influence any association detected.

4.4.2.2 Matching technique

Having chosen the criteria on which participants will be matched, the technique by which participants will be matched must be chosen. Matching can either be performed subject-by-subject (individual matching) or for groups of participants (frequency matching).

Individual matching allows each participant to be matched exactly based upon either continuous variables, such as exact age, or categorical variables such as age bands. Whilst this may appear preferable, individual matching may reduce the population of the study since cases cannot be included if there are no suitable controls available. Each exposed case is matched to a set number of unexposed controls, or the number of controls can be allowed to vary between cases. In an ideal situation, the statistical power of the study is increased by increasing the number of controls per case up to four controls per case, but beyond this the additional gain is small. (Miettinen, 1969)

Frequency matching involves matching an entire stratum of control subjects with an entire stratum of cases based on the matching factors. For example, if cases and controls are to be matched by age and gender then the case group might be divided into four groups; women <45 years old, women ≥45 years old, men <45 years old and men ≥45 years old. The proportion of cases in each of these groups could then be determined and a similar proportion of controls sampled from each strata. (Szklo & Nieto, 2014) Since the cohorts of cases and their controls are only required to have a similar distribution of strata defined by matching factors across the whole group e.g. similar proportion of males and females, rather than the individual characteristics of each case being required to exactly match those of their controls, exclusion of participants at the matching stage is minimised.

Using either technique for matching, residual confounding cannot be eliminated, with risk particularly high where the matching variable is a confounder, necessitating careful thought when choosing matching criteria.

In this study, frequency matching would increase inclusion of cases and controls, as the matching criteria chosen (year of birth, gender and registered general practice) must all be met exactly. Matching by registered general practice (each of which has a geographically defined region within which patients must reside in order to register with that practice) is likely to be the most limiting factor, reducing the pool from which each control can be chosen to the size of the registered patient list of the general practice at which the case is patient. Matching individually would require there to be four or more patients on that practice list of the same gender, and having been born in the same year, who did not have gout. Matching by registered general practice is intended to minimise the impact of the

socio-demographic factors on the association of interest, however there can be considerable differences within one practice area. In the case of individual matching this may simply mean that an extremely restrictive matching criteria has been applied with little benefit, however where these differences are magnified across strata during frequency matching, even this crude measure of socio-demographics may become unreliable.

Since no additional socio-demographic information was available on the individual participants, matching by registered general practice was the only method available of accounting for socio-demographic status. Thus, to avoid the magnification of intra-practice boundary differences in socio-economic characteristics, individual matching by age (year of birth), gender and registered general practice at a ratio of four participants without gout, to each participant with gout, was selected as the method for this study.

4.5 Sources of error in cohort studies

There are two major sources of error that a cohort study may be susceptible to; random error and systematic error (also known as bias). Both may contribute to erroneous findings and will be discussed below.

4.5.1 Random Error

Random error results in imprecise study findings resulting from variation within the study population due to chance alone. There are a number of sources of random error which include random variation in the sampling of study subjects, genuine unexplained biological variation in occurrence measures between subjects, and mismeasurement of study variables. These chance deviations may result in less

precise results and therefore reduce the power of the study to detect a true association, causing the null hypothesis to be falsely rejected (Type I error) or accepted (Type II error).

Since random error affects precision by contributing to variance of measurements or estimates, measures to reduce the effect of random error must mitigate against this variance. Since variance can be reduced by increasing the size of the study, sample size must be adequate and take into account the required level of statistical significance of the expected result, the acceptable chance of missing the real effect, the magnitude of the effect under investigation, the amount of disease in the population and the relative sizes of the groups being compared in order to achieve the desired precision of the study.

4.5.2 Bias

Bias has been defined as “deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of the data that can lead to conclusions that are systematically different from the truth.” (Last, 2001)

There are many forms of bias that a cohort study may be susceptible to, but all represent a systematic error leading to a consistent over or underestimation of results. Random error may also contribute to erroneous results, but these errors are caused by factors that may vary from one error to the next, and may be due to chance, rather than a deficiency in the study design or conduct itself. Random error may produce less precise results and therefore reduce the power of the study to detect a true association, but it does not produce a consistent systematic inaccuracy in the results.

Many forms of bias have been described. The major classifications relevant to the investigation of this association are selection bias and information bias.

4.5.2.1 Selection Bias

Selection bias is defined as error due to systematic differences in characteristics between those who take part in the study and those who do not. (Last, 2001) In this study which uses EHR, only those who consult with gout are eligible for inclusion as cases. At the milder end of the disease spectrum, there may be patients who do not consult their GP with their symptoms, or manage their gouty symptoms with over-the-counter medications; therefore presence of those symptoms would not be recorded in the EHR, resulting in these patients not being eligible for inclusion. Furthermore, since the definitive diagnosis of gout requires aspiration and examination of synovial fluid to determine the presence of MSU crystals, (Zhang et al, 2006b) a procedure not readily accessible to general practitioners who make the diagnosis on clinical grounds, there is the possibility of diagnostic inaccuracy and therefore ascertainment bias. Ascertainment bias is a bias which results in unequal representation of different classes of cases or participants within a sample. It can be caused by selection of participants from specialised populations, such as secondary care gout clinics, or by the diagnostic techniques used to identify the condition. Thus it may be that patients who present with the most severe or typical symptoms rendering diagnosis of gout obvious are over-represented, whilst those who present with atypical or rarer symptoms of the condition are under-represented since the clinical diagnosis is more difficult. Whilst clinical diagnosis of gout in primary care has been shown to

be reliable, (Roddy et al, 2007; Roddy et al, 2010) the possibility of ascertainment bias cannot be excluded.

The technique used to retrieve data from EHR within large databases can also predispose to selection bias, since identification of diagnoses relies upon the use of a library of codes which correspond to those diagnoses. Correct identification of these codes in searching for patients with gout is crucial in ensuring that all potentially eligible patients are identified, for example if a commonly used code for gout is omitted from the list of codes used to identify gouty patients then there may be a large proportion of patients with gout who are eligible for inclusion in the study but are not identified as such. Similarly, such an omission may result in participants appearing eligible for inclusion in the non-gout group, when in fact they do have gout that has been recorded using a code omitted from the list. This also extends to the identification of co-morbidities since, for reasons discussed in Chapter 5, all participants were required to be free of vascular disease at entry into the study. If the codes used to identify these vascular diseases within the patients electronic medical record were incorrect, this could result in the inclusion of patients with prior vascular disease that has not been identified, potentially increasing any association detected, or the exclusion of patients without a history of vascular disease who should have been eligible for inclusion rendering the sample unrepresentative.

4.5.2.2 Information bias

Information bias is defined as “a flaw in measuring the exposure or outcome data that results in different quality (accuracy) of information between comparison

groups". (Last, 2001) The form of information bias most relevant to this study is misclassification bias.

Misclassification bias is a systematic error whereby participants are attributed a value or category other than that to which they should have been assigned, (Last, 2001) for example if inaccurate codes are used to identify incident vascular events, participants may be identified to have the outcome of interest when in fact they do not, perhaps leading to the detection of a spurious association. Similarly, the use of EHR relies on the accurate coding of events by clinicians. If coding is inaccurate, inconsistent, or too vague using symptom-based rather than diagnostic codes (e.g. coding onset of angina as "chest pain", for which there are multiple non-vascular causes) then events of interest may not be identified and thus the magnitude of an association systematically underestimated.

4.5.2.3 Techniques used to minimise bias

Although bias can never be completely eliminated in any study, it must be considered in the study design with the aim of minimising the impact on the study findings.

As described above, accurate identification of cases for inclusion as gout participants, those participants with prior history of vascular disease, and participants who experienced the vascular outcomes of interest was of the utmost importance to the accuracy and generalisability of the study findings. For this reason it was initially hoped to use previously validated lists of codes to identify gout and vascular disease within the CPRD, however these were not available. A

rigorous process of identifying diagnostic codes for gout, vascular disease, and all of the potentially explanatory covariates of interest was undertaken.

Our lists of codes for outcomes were created in a systematic way, based upon the Read coding system which underpins all EHR database coding in the UK. Read codes are divided into chapters relating to the relevant organ systems, and codes are hierarchical in their specificity. All relevant chapters of Read codes were collected and each code individually considered for inclusion by Dr Lorna Clarson (GP), Dr Samantha Hider (PhD lead supervisor, Senior Clinical Lecturer in Rheumatology and Honorary Consultant Rheumatologist) and Professor Christian Mallen (PhD co-supervisor, Professor of General Practice Research and GP). Consensus was then reached on final codes to be included and records individually checked by Dr Lorna Clarson to ensure that in those where an event was identified it was the incident event, and other codes had not previously been used that were not on the list. Records for 50 of those patients in whom an event was not identified were also checked by Dr Lorna Clarson to ensure that no vascular events of interest had been recorded using codes not in the list and therefore missed. This exercise was repeated for each type of vascular event until all were satisfied that the lists were complete.

Although a formal chart validation study would have been helpful, this was not possible due to the nature of the primary care data, and had already been performed to evaluate validity of coding of cardiovascular outcomes in CPRD, reporting a positive predictive value of diagnosis of MI coded in CPRD of over 80%, and comparable reliability of coding for ischaemic heart disease to other primary care databases. (Khan et al, 2010a) The data did not contain data from

secondary care records in order to verify that the Read code corresponded to a correct diagnosis made in hospital.

4.6 Analysis of Cohort Studies

In cohort studies participants exposed to specific risk factors (e.g. gout) are compared to those who are unexposed. The aim of the analysis undertaken must therefore be to best estimate risk of the outcome (dependent variable) based upon a set of exposures (independent or explanatory variables), in a clinically interpretable model. (Hosmer et al, 2013)

Regression techniques are used to fit a model predicting the outcome as a function of the explanatory variables. This regression can take many forms; linear where the outcome variable is assumed to be continuous, logistic regression where the outcome variable is binary, Poisson regression where the outcome variable is a count (e.g. number of events) and proportional hazards regression where time to event is the outcome of interest. Since in this study the outcome of interest is risk of vascular event, including the time to event, the most appropriate technique to use is survival analysis using Cox proportional hazards regression.

4.6.1 Proportional Hazards Regression

Proportional hazards regression is a technique used when the outcome of interest is time to a particular event of interest, calling this “survival time”, and thus this type of analysis is often referred to as survival analysis. Survival time may describe time until death, although use of the technique has been extended to

include other outcomes such as healthy time survived from diagnosis of a condition until incidence of a particular event, e.g. complication or exacerbation. This study aims to estimate the excess risk of vascular disease in patients with gout, compared to those without gout. This risk can be calculated either with or without taking into account the time that individuals remain in the study. For this study (detecting incident vascular events) it was decided that not only was the number of events of importance, but that time to vascular event from diagnosis of gout (or equivalent “index date” for controls) was also a relevant outcome measure.

Survival analysis is a specific approach which allows study participants who do not experience the event of interest, or are lost to follow up during the study, perhaps by transferring out of the area, to be taken account of in the analysis. Furthermore, survival data are rarely normally distributed and so simple analysis such as taking the mean of survival time is not appropriate.

In analysing survival data, two functions that are dependent on time are of particular interest: the survival function and the hazard function. The survival function S(t) is defined as the probability of surviving to at least time t. The hazard function h(t) is the conditional probability of dying at time t having survived to that time.

Patients are classified at each time point as:

- having experienced the event of interest
- being at risk of the event
- censored (e.g. having died or lost to follow up)

This model uses the assumption that the prognosis for censored and surviving patients is the same, and that events happen contemporaneously with their recording.

The graph of S(t) against t is called the survival curve. The Kaplan-Meier method can be used to estimate this curve from the observed survival times without the assumption of an underlying probability distribution. This method is based on the basic idea that the probability of surviving k or more periods from entering the study is a product of the k observed survival rates for each period (i.e. the cumulative proportion surviving). (Kaplan & Meier, 1958) The limitation of the Kaplan-Meier method is that it is limited to univariate analysis and cannot take account of multiple contributory factors or confounding influences.

The Cox Proportional Hazards (CPH) model can be used to model response in the event hazard function to potential explanatory covariates, and assess the influence of that particular variable on the likelihood of developing an incident event over time. (Cox, 1972) The CPH model estimates the baseline hazard nonparametrically, meaning that no inappropriate statistical distribution (e.g. normal distribution) is attributed to survival data, and several key assumptions underpin this model.

- *There is a baseline hazard function which is constant* and common to all the subjects in all of the groups for comparison. Each group has a hazard function that is a positive multiple of this baseline hazard and covariates act only on this group-specific hazard function and not the baseline hazard.
- *The assumption of proportional hazards* whereby, although there is no assumption made about the probability distribution of the hazard, it is

assumed that if the risk for dying at a particular point in time in one group is, for example, twice that in the other group, then it will also be twice that of the other group at any other time point, i.e. the hazard ratio does not depend on time.

- *Censoring is non-informative*, meaning that censoring is independent of the outcome of interest and, for example, if the outcome of interest is mortality, patients are not removed from the study just prior to death.

4.6.2.1 Assumption of proportional hazards

Schoenfeld residuals were first proposed in 1982, and are used to assess goodness-of fit of the proportional hazards regression model. (Schoenfeld, 1982) Rather than a single residual for each individual, there is a separate residual for each individual for each covariate, and these residuals are independent of time. Thus regressing residuals against time should show a random pattern, confirming this independence from time, and thus satisfaction of the proportional hazards assumption.

Where the assumption of proportional hazards is not satisfied it suggests that in that particular statistical model the hazard ratio changes over time and this technique allows assessment of which of the covariates within the model may vary over time resulting in the overall change in difference in risk between groups. These covariates can then be re-entered as time-varying covariates in order that the model as a whole can satisfy the assumption of proportionality.

4.6.2 Multilevel Discrete-time Event History Analysis

An alternative way to analyse data where covariates are likely to vary with time is to analyse the data using time windows of a specified length and to record a value of the covariate in each time window. Whereas using the CPH regression model time is essentially treated as a continuous variable, Multilevel Discrete-time Event History Analysis (MDtEHA) is a form of regression allowing follow-up time to be divided into discrete intervals (e.g. years following diagnosis of gout) until the occurrence of an event of interest, or the patient is censored. Each time interval contains a binary indicator of whether an event of interest has occurred during that window of time. This method of analysis allows a discrete time hazard function to be generated for each time window, that is, the probability of having an event during that interval, given no previous occurrence. (Allison, 1984)

Having these individual windows of follow up also allows a more realistic examination of the effect of covariates of interest, since these can be allowed to vary in each discrete time window, and change in these covariates throughout the follow-up can be used to estimate the contemporaneous association between the change in that covariate and probability of experiencing the outcome of interest. Thus if a patient is to develop a new risk factor or incident comorbidity predisposing to the event of interest, or receive a new prescription for a medication potentially protecting against the event of interest, then the effect of this new covariate within that time window can be taken into account in the overall estimate of risk.

The resulting odds ratio reflects the risk of experiencing an event of interest associated with each individual covariate across all participants, and are

interpreted in the usual way regarding continuous or categorical predictors. This form of analysis therefore also differs from CPH regression in that it estimates the odds ratio of occurrence of the event of interest associated with each particular covariate, across all participants, as opposed to a hazard ratio.

Advantages of MDtEHA include:

- Assumption of proportional hazards does not need to be satisfied
- Can take account of covariates which change during follow-up

Disadvantages of MDtEHA include:

- Manipulation of data is required in order to be able to fit such models
  - Each patient must have at least a binary indicator of presence/absence of the event of interest for each discrete interval of time until they either experience the event of interest or are censored.
  - This requires manipulation of a dataset from the format in which continuous-time survival analysis is applied, from one row of data per participant, to a row of data for each time window for each patient until the event of interest occurs or they are censored
  - If there are many covariates of interest, or multiple short time windows a large dataset can result, resulting in slow, difficult computation of the data

4.6.3 Important differences between CPH regression and MDtEHA

There are several important differences between CPH regression and MDtEHA. Understanding these differences is key to understanding the estimates of risk produced using the two different techniques, and the reasons behind the application of both. The most important of these differences are listed below:

1. CPH regression estimates the difference in risk between two groups (e.g. exposed to gout compared with unexposed), whereas MDtEHA does not compare groups but rather estimates the probability of any participant (exposed or unexposed) experiencing an event of interest associated with each covariate in the model. Thus proportional hazards regression estimates hazard ratios whilst MDtEHA estimates odds ratios
2. Covariates in a CPH regression are measured at baseline (the diagnosis of the condition of interest, or matched date for controls), whereas MDtEHA allows use of the data on covariates in post-baseline follow-up to be used to estimate overall risk, therefore accommodating changes in co-morbidities, prescriptions or lifestyle choices (e.g. giving up smoking).
3. Presence of covariates recorded at baseline is presumed to be a constant contribution to risk of event of interest using CPH regression, in contrast to MDtEHA where covariates can only contribute to the overall estimate of risk in time windows where a value is recorded.
4. Cox regression depends on the proportional hazards assumption being satisfied. There are discrete time models that do not invoke the proportionality assumption, but we can still ask whether a predictor's effect

is constant or if it varies over time.For a binary time varying covariate such as statin use, the regression estimate contrasts the population *logit* hazard for people who have taken statins with those who have not.

4.7 Summary

This chapter has discussed the choice of a retrospective cohort study design utilising pre-existing data from a large database of primary care EHR to examine the association between gout and vascular disease. It has also identified selection and information bias as important considerations in the study methods, and describes the techniques of Cox Proportional Hazards Regression and Multilevel Discrete Time Event History Analysis which will be used in the analysis of the data.

Chapter 5: Study Methods

5.1 Overview

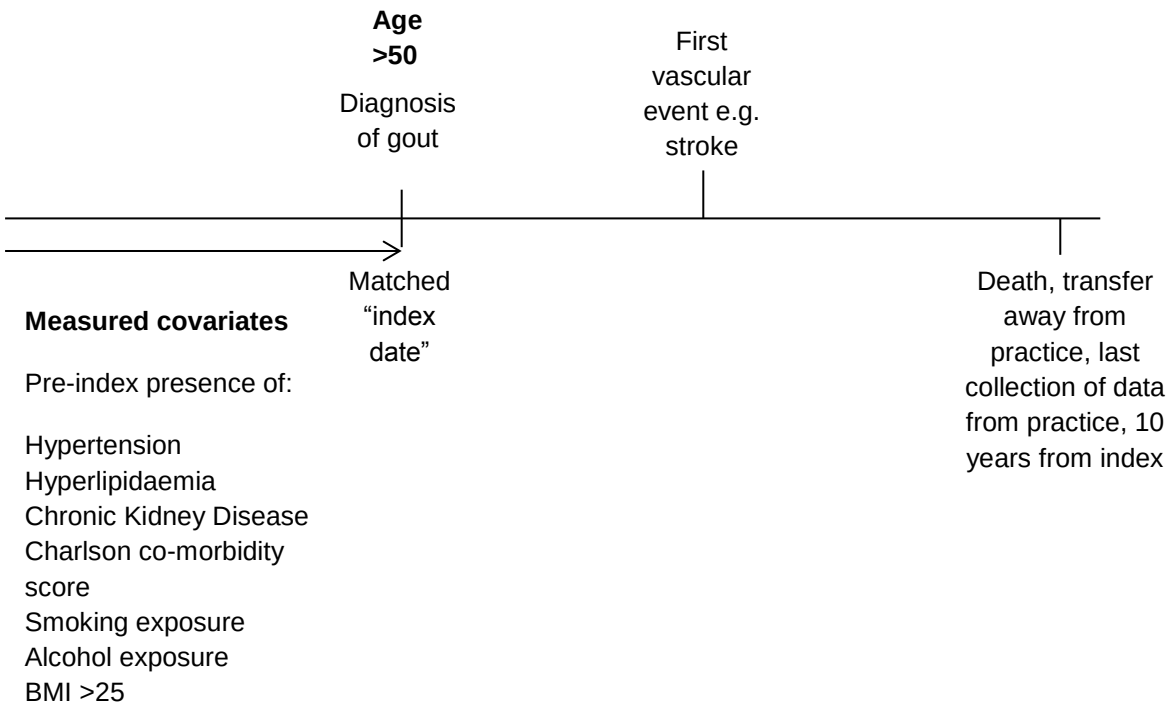
Chapter 4 introduced the retrospective cohort study, its advantages and disadvantages, and previous uses in this context. This chapter will discuss the application of this methodology to the investigation of the association between gout and vascular disease. The final study design, study population and its source, data handling and statistical analysis are described in detail.

5.2 Overview of study design

This study uses a retrospective cohort design, comparing the risk of developing vascular disease between a cohort of gout cases and a cohort of age, sex and practice matched controls. Data from the UK Clinical Practice Research Datalink (CPRD) were examined for 8386 patients diagnosed with gout between 1987 and 1999, matched with 39,869 age-, gender and GP practice matched controls. All had no previous history of vascular disease in order to investigate the relationship between gout and incident vascular disease. This was important for two reasons, firstly that a prior vascular event itself can be considered a risk factor for a further event, and secondly that the ongoing routine monitoring associated a pre-existing diagnosis of vascular disease would introduce surveillance bias.

Incident cardiovascular, cerebrovascular and peripheral vascular disease was identified in the following ten years from the baseline consultation for gout, or a matched “index date” equivalent to the date of the baseline consultation for controls. Figure 5.1 shows a pictoral representation of the study.

Figure 5.1: A pictoral representation of the study



5.3 Study population

5.3.1 Clinical Practice Research Datalink

The CPRD is the largest database of primary care EHR in the world, containing anonymised data for approximately 8% of the population of England and Wales (over 12 million patients, 5 million of whom are active patients. This data set was established in 1987 and was formally known as the General Practice Research Datalink (GPRD). (Tate et al, 2014) Currently over 650 general practices contribute nationally representative data. (www.cprd.com/intro.asp last accessed 14/06/2014) The high validity of diagnosis in the CPRD has been reported by two

systematic reviews, with correct diagnosis confirmed in a median of 89% of cases for 183 diseases. (Herrett et al, 2010; Khan et al, 2010a)

A typical patient record might contain demographic information as well as information on each episode of care, including a diagnostic Read code describing the main reason for the contact, results of examinations and investigations, prescriptions and onward referrals. Read codes are a coded thesaurus of clinical terms, used to record each contact in general practice records. Entries are numerically coded allowing for easier identification.

5.3.2 Previous use of the CPRD

Between 1995 and 2009, the CPRD has been used in over 700 published studies. Validity of CVD diagnoses in CPRD, or the extent to which diagnosis of CVD in CPRD is likely to represent an accurate diagnosis of CVD, or be similarly recorded in an alternative similar database, was assessed by a recent systematic review. A positive predictive value of diagnosis of myocardial infarction and cerebrovascular disease coded in CPRD of over 90%, and comparable reliability of coding for ischaemic heart disease to other primary care databases such as the Doctors' Independent Network (DIN), a separate UK primary care database which collects data from over 300 non-CPRD practices, was reported. (Herrett et al, 2013; Khan et al, 2010a)

The CPRD has been used to study the risk of vascular disease associated with numerous conditions. Table 5.1 summarises a selection of the most recent.

Table 5.1: Summary of studies using the CPRD to examine relationships between vascular disease and other medical conditions

Authors	Year of Publication	Association examined
(Mehta et al, 2010)	2009	Psoriasis and cardiovascular mortality
(García Rodríguez et al, 2010)	2010	Chronic obstructive pulmonary disease, heart failure, myocardial infarction, lung cancer and death
(Schneider et al, 2010)	2010	Chronic obstructive pulmonary disease and cardiovascular disease
(Solaymani-Dodaran et al, 2008)	2008	Primary biliary cirrhosis and cardiovascular and cerebrovascular events
(Soedamah-Muthu et al, 2006)	2006	Type 1 Diabetes and cardiovascular disease
(Smeeth et al, 2004)	2004	Inflammatory states and myocardial infarction and stroke
(Watson et al, 2003)	2003	All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis

5.3.3 Identification of Participants

In order to search CPRD data, numerical codes must be identified relating to the condition of interest. In this study these codes were identified using a browser supplied by the CPRD. The browser could be searched with free text, or wildcard entries. Wild card entries allowed entries to be identified that contained words of interest within them, for example, a wildcard entry for "vascular" would return entries for cardiovascular, cerebrovascular etc.

Gout case identification

The CPRD identified gout cases using codes returned by the CPRD browser and listed in appendix 2. Only patients aged over 50 at time of first diagnosis for gout were included to prevent the inclusion of patients with rare genetic causes of gout (e.g. Lesch Nyhan syndrome) that may further predispose them to vascular disease. Lists of codes identifying vascular disease were used to identify and exclude any patients with a pre-index history of vascular disease (listed in Appendix 2). The date of first ever consultation for gout was taken as the "index date", and records examined for vascular outcomes of interest over the next 10 years.

Control (non-gout) identification

Controls were matched by year of birth, gender and registered general practice, with an average minimum of 4:1 control to case ratio, this ratio having been selected for reasons stated in Chapter 4.4.2 previously. Matching of five controls to one case was undertaken in order to maintain statistical power, despite the likelihood that some patients may need to be excluded for a variety of reasons,

such as evidence of pre-existing vascular disease or large amounts of missing data. Lists of codes for gout, hyperuricaemia, and vascular disease were used to identify and exclude controls with any pre-index history of those conditions (see Appendix 2). The control patients were assigned an index date equivalent to the date of first consultation for gout of the gout patient to which they were matched, records were then examined for outcomes of interest over the next 10 years.

5.3.4 Matching procedure

The process of matching control subjects with gout patients was undertaken by the CPRD using their standard procedure for matching, but using our specified matching criteria. The potential control subjects were stratified by primary care practice, year of birth and gender, and up to five control subjects were randomly selected from the appropriate stratum for each gout patient.

5.4 Known vascular disease risk factors

Vascular disease has many contributory factors, including medical conditions such as diabetes and hypertension, and lifestyle factors such as smoking and alcohol consumption.

Vascular risk factors of interest were chosen *a priori* by discussion between GPs and rheumatologists on the basis of being considered clinically relevant and measurable, and representative of traditional risk factors for vascular diseases

described in the literature. They included gender, presence of hypertension, hyperlipidaemia and chronic kidney disease, and measures of age, body mass index (BMI), ever/never exposure to smoking/alcohol, and ever/never exposure to prescribed statins or aspirin at baseline (date of diagnosis of gout or matched index date for controls). Use of anti-hypertensive medication was not used as an indication of history of hypertension since many anti-hypertensives are also used for alternative clinical indications, for example both beta-blockers and calcium channel blockers can also be used for cardiac arrhythmias and prophylaxis of chronic headaches.

Charlson Co-morbidity Index at baseline was also calculated using a technique described by Khan et al. (Charlson et al, 1987; Khan et al, 2010b) The Charlson co-morbidity index is a weighted index taking account of the number and seriousness of co-morbid conditions to predict one year mortality. (Charlson et al, 1987) The presence of relevant conditions was identified by searching pre-index patient records using lists of codes (listed in Appendix 2). A list of CPRD codes which allowed identification of relevant conditions and their weights within the EHR had been previously prepared by Kahn et al, 2010, (Khan et al, 2010b) the weights of these conditions were then added together to create an overall co-morbidity score for each participant, and this was entered as a continuous variable. Lifestyle factors were recorded in a separate coded file and this was searched for relevant information on smoking, alcohol consumption and BMI.

The matching variables were also entered into the analysis as explanatory covariates, in order to remove variability due to the matching variable and ensure

a more accurate estimation of the strength of the association. (Bland & Altman, 1994)

Data was recorded on smoking status for 70% of participants, alcohol consumption for 80%, and BMI for 76% of all participants. In order to minimise the effect that the missing data would have on the size of the dataset available for analysis, these variables were categorised into ever/never exposure to smoking and alcohol, and overweight yes/no (BMI >25) with a “missing” category for each. The decision was made not to undertake imputation, a technique by which missing data is replaced to avoid deletion of cases which have missing values. This deletion reduces the power of the study, and imputation can be considered if the data is missing at random. However, since a database of primary care EHR is being used as the data source, and the data held within these records is collected by healthcare professionals, it is entirely possible that missing data is not missing at random but in fact there are underlying reasons why it has not been collected, for example, lack of BMI recording in those who are obese due to difficulty in broaching this issue with the patient. In this case imputation would introduce bias and was therefore not used. (Taylor et al, 2013)

Physical activity and family history of cardiovascular disease were not included in the model despite being recognised vascular risk factors, since these characteristics were only recorded for the minority of patients. Level of physical activity was recorded in 41.8% and family history of cardiovascular disease in 12.3%.

Further discussion of how these potential explanatory variables were entered into the statistical model can be found in section 5.6.4.

5.5 Vascular outcomes of interest

Vascular events of interest were identified by searching post-index records using lists of codes designed to identify particular outcomes (see Appendix 2). The outcomes of interest are shown in table 5.2 below

Table 5.2: Outcomes of interest

Cardiovascular Disease	Cerebrovascular disease	Peripheral Vascular Disease
All cardiovascular events (codes which indicated incident ischaemic cardiac events, but were not sufficiently specific to allocate to either angina or MI)	All cerebrovascular events (codes which indicated incident cerebrovascular events, but were not sufficiently specific to allocate to either TIA or CVA)	Any peripheral vascular disease
Angina	TIA	
Myocardial infarction	CVA	
CVA = cerebrovascular accident; MI = myocardial infarction; TIA = transient ischaemic attack;		

The date of the first vascular event was recorded and time to event from baseline was calculated. It was decided to use the first vascular event only, as having had one vascular event increases risk of subsequent events which may exaggerate risks attributable to gout.

5.6 Statistical methods

This section describes the statistical analysis performed in the study.

Data were analysed using SPSS Statistics version 20.0 (SPSS Inc, IBM Corp; 2012) and Stata statistical software release 12 (StataCorp: College Station, TX, 2011)

5.6.1 Descriptive statistics

Descriptive statistics were used to explore similarities and differences in gout and non-gout groups at baseline. Age and gender distribution, and frequency and percentage of co-morbid conditions allowed validation against the wider gout population to establish the generalisability of the study results.

5.6.2 Cox Proportional Hazards Modelling

Proportional Hazards Regression as described in section 4.6.1, was used to thus estimate the risk of vascular disease in those exposed to gout, compared to those who were not, taking into account time in the study.

5.6.3 Censored events

The principles underlying survival analysis were developed to take account of subjects within populations who do not go on to develop the event of interest

during the follow up period, or who are lost to follow up, and consequently, for whom, survival times cannot be known. This is termed “censoring”.

Within this study, in the absence of a vascular event, patients were censored at the earliest of the following time points:

- 10 years from their index consultation for gout
- Transfer out of the practice contributing their records to the CPRD
- Death (not due to a vascular cause)
- Last collection of data from the practice contributing their records

This constitutes “right censoring” and, in the case of those who reach 10 years post diagnosis of gout without a vascular event, assumes that events in these individuals (if they were to occur) were beyond the end of the study follow-up period. In the event of death from a non-vascular cause, the individual is no longer at risk of a vascular event and their contribution to the study ends at the point at which they are censored. In those participants who transfer out of the practice contributing their records to the CPRD, or whose last record is prior to 10 years from their diagnosis of gout, survival time cannot be known and so they are censored at that point. Follow-up was censored to 10 years as fewer participants had records longer than this which would skew the estimate of risk.

It was decided not to allow participants who had experienced cardiovascular events to remain “at risk” of cerebrovascular events where this was the outcome of interest, for the same reason that we excluded participants with a prior history of vascular disease, that is a prior vascular event predisposes to further vascular

events, and in the example above it would not be possible to ascertain that the risk estimated was that of truly incident cerebrovascular disease in gout.

5.6.4 Explanatory Covariates

There are many factors which contribute to the risk of developing vascular disease. These can include medical conditions such as hypertension or hyperlipidaemia, or lifestyle factors such as smoking and alcohol consumption. In order to establish the role that various factors play in the risk of developing vascular disease after a diagnosis of gout, two models were designed.

Model 1 was designed to minimise surveillance bias (i.e. detection of vascular disease resulting from routine monitoring for another condition) and assess the risk of vascular disease in gout patients presenting to the GP for the first time, i.e. only introducing covariates into the model that might be known prior to further examination or investigation by the GP. Potential confounders introduced in Model 1 included age at baseline, gender, categorical variables for ever/never exposure to smoking and alcohol, and yes/no for overweight (BMI >25), and continuous Charlson Co-morbidity Index score. **Model 2** was designed to assess risk of vascular disease taking into account all potential confounders. Covariates introduced into Model 2 included all of those in Model 1, with the addition of presence at baseline of hypertension, renal disease and hyperlipidaemia, and dichotomised values for statin and aspirin consumption (categorised as ever/never prescribed). Presence of diabetes was not included separately since this forms part of the Charlson score.

Potential explanatory covariates of interest had been identified *a priori,* and thus all were included into the statistical model to determine the adjusted effect of each risk factor on the outcome. If, after adjustment, gout as a risk factor maintains a statistically significant association with the outcome, it can be considered an independent risk factor for the vascular event in question. (Brotman et al, 2005)

5.6.5 Assumption of proportional hazards

Since proportional hazards regression requires the assumption of proportionality (that any increased or decreased risk found in one group compared with another remains proportionally similar over time), this assumption was tested for each covariate.

The validity of the assumption of proportional hazards was assessed using Schoenfeld residuals and Stata's own diagnostic test. Where this assumption of proportionality was violated (suggesting the risk associated with potential explanatory covariates may vary over time) the relevant variables were re-introduced into the model as time-varying covariates, thus allowing the proportional hazards assumption for the association between gout and the vascular outcome in that particular model, to be satisfied. (Bellera et al, 2010)

Robust standard errors (also known as heteroskedasticity-consistent standard errors) were used to try to improve the precision of the estimate of risk since this study was of a matched design. Where variance within a sample population is not equal (heteroskedasticity), standard errors are liable to be unduly influenced by outliers, and thus reduce precision of the estimate. In matched studies, where

there may be clustering i.e. observations within groups of exposed gout patients and their unexposed matched controls may be correlated in some unknown way, it is likely that standard errors may not be independently and identically distributed. In this situation it is recommended that a robust estimator, such as the White-Huber estimator, is used, since this technique is considered more resistant to the effect of outliers. (Huber, 1972)

5.7 Subgroup analysis and Interactions

The risk of vascular events was investigated by gender subset (since both gout and vascular disease are more common in men), (Roddy & Doherty, 2010; Rossouw, 2002) and over different time periods following the diagnosis of gout, by limiting follow-up to 1 year, 2 years and 5 years post index date. Risk over different time periods was investigated to add clinical utility to the findings of the study, allowing trends or peaks in risk to be identified and thus identify optimum points at which screening for or management of vascular risk factors should be implemented. Time points were chosen to reflect potentially clinically relevant points in the time-course of gout; within one year of diagnosis to estimate initial risk of vascular disease associated with transition from asymptomatic hyperuricaemia to gouty arthropathy, within two years since initiation of urate-lowering therapy (ULT) requires at least two attacks per year, and so any impact of ULT would not be seen until two years following diagnosis of gout, and five years estimates risk at the study mid-point.

5.7.1 Interactions

When investigating the relationship by subset, interactions must be considered. An interaction describes a situation where the effect of one variable on the dependent variable is influenced by the value of another variable in the model; for example, whether risk of vascular event in participants with gout is influenced by gender. In the absence of significant interactions it is appropriate to present an overall estimate of the effect of gout on the risk of vascular disease (the main effects). Where an interaction is significant the main effects cannot be interpreted in the usual way since this effect is different in men and women. In this situation the results must be presented by gender (the simple effects), since the effect of gout varies by gender.

Where there are two variables to be considered, as here with the effect of gout and gender on risk of vascular disease, the product of the two variables is introduced into the model in order to assess the significance of any interaction. Where there are more than two explanatory variables, several interaction terms are created.

The influence of follow-up time on the gout effect was found to be non-significant using Stata's own test of proportional hazards ($\chi^2_{(1)}$ =0.82 p=0.05). The only significant interaction was that between gout and gender.

5.7.2 Significance of Interactions

In order to test the significance of the interaction terms the Wald test was chosen, since where there is potential for clustering (such as that induced by matching) the likelihood used for estimation does not reflect the true distribution of the sample since observations are no longer independent. For this reason the likelihood ratio test cannot be used. The Wald test compares the result of the parameter estimate divided by the estimated standard error of the parameter at this value, all squared, with the chi-squared critical value at one degree of freedom, with 95% confidence, which equals 3.84. If the Wald statistic value is greater than 3.84, then the interaction term was considered significant in the model. (Gould et al., 2006)

Where interaction terms were found to be significant, stratified effect sizes were calculated in order to clarify differences, using the STATA LINCOM command, a post-estimation command that can be used to calculate the appropriate linear combinations from the model containing the interaction. This has the added advantage of using all the data rather than fitting separate models for gender. (Collett, 1994)

5.7.3 Multilevel Discrete Time Event History Analysis

In order to estimate the overall risk of vascular events, but also accommodate changes in presence or absence of co-morbidities, medications or lifestyle related risk factors (e.g. giving up smoking, or losing weight) during follow-up, MDtEHA was used. Time following diagnosis of gout was divided into discrete windows of one year, and EHR from that period examined for data on covariates of interest,

since many of the covariates of interest in this model were subject to variation over time. Some, such as gender, do not vary, whilst age will inevitably vary with time elapsed since diagnosis. Others, such as BMI, blood pressure, incidence of comorbidities and prescription for aspirin and statins not present at baseline may vary during follow-up and this variation may influence risk of vascular event. Data collected during follow-up is not used in this way in the Cox Regression analysis since all covariates of interest are measured at baseline, and not subsequently. Thus gout/non-gout status was entered into the model, alongside values (present/absent or categorised) for covariates of interest in each year-long time window, into an MDtEHA logistic regression model (since the outcome of interest is a binary one). This model is used to estimate the odds of experiencing an incident vascular event associated with each covariate.

The covariates used were slightly different to those used in the continuous model. They included age, gender, presence of hyperlipidaemia or renal disease, continuous Charlson co-morbidity score, measure of blood pressure (categorised into normal ≤150/90; high > 150/90 or missing), measure of BMI (categorised into normal ≤25; high > 25kg/m^2 or missing) and prescription of aspirin or statins. Since individual blood pressure measurements could be identified and included as covariates in each time window, diagnosis of hypertension was removed from the model to avoid overadjustment.

An interaction between gout and gender was tested as this was found to be significant in the continuous model. An interaction term for this gout*gender interaction was also included and the STATA lincom post-estimation command

was used as described in 5.7.2 to estimate the effects of gout exposure within gender.

5.8 Summary

This chapter has described the application of the retrospective matched-cohort study methodology to the investigation of the association between gout and vascular disease used.

It has described the derivation and validation of a dataset of EHR from the CPRD used for the study, and discussed the statistical methods of CPH regression and MDtEHA applied in analysing these data. This chapter has also described the methods used to investigate the effect of gout-specific characteristics, such as medication use (using defined daily dosage to compare the effect between groups), consulting behaviour and compliance with urate lowering therapy, on risk of incident vascular disease.

Chapter 6: Results

6.1 Overview

This chapter will present the results of the cohort study.

The baseline demographics and pre-existing comorbidity of the cohort are described, followed by the results of both the continuous and discrete-time survival analysis comparing risk of incident vascular disease in patients with gout to those without.

6.2 Baseline data

This section will describe the characteristics of the study population, including gender distribution and age at date of diagnosis of gout (inclusion criteria required patients to be aged 50 years or over at the time of diagnosis of gout). These data are shown in table 6.1.

Table 6.1: Participant demographics at baseline

	Gout	Non-gout	p for significance
Participants, n	8386	39766	
Age at diagnosis (S.D), y	66.3 (+/- 10.8)	66.2 (+/- 10.7)	0.99
Male, %	69.4	69.2	0.70
Ever smoker (missing), %	28.3 (23.1)	26.2 (31.2)	<0.01
Ever drinker (missing), %	73.5 (13.8)	64.4 (21.2)	<0.01
BMI >25kg/m^2 (missing),%	59.7 (18.3)	43.6 (25.0)	<0.01
Hypertension, %	36.0	17.3	<0.01
Hyperlipidaemia, %	5.7	3.2	<0.01
Diabetes, %	4.2	4.4	0.33
Chronic kidney disease, %	1.4	0.2	<0.01
Ever statin use, %	34.3	25.6	<0.01
Ever aspirin use, %	42.7	33.4	<0.01
S.D.= standard deviation			

6.3 Frequency of vascular outcomes

This section reports the frequency, percentage and median time to first vascular event outcomes within the gout and control groups, subdivided into particular vascular outcomes.

6.3.1 Number of vascular events

There were a total of 11,266 vascular events during follow up. The number of events by outcome is summarised in table 6.2 below, presented as median time to event and interquartile range (IQR).

Table 6.2: Frequency, percentage and median time to first vascular event outcomes within each group

Vascular Event	Gout (n=8386)	Median Time to event* (months)	IQR	Not gout (n=39766)	Median Time to event* (months)	IQR
All vascular events (n=11266)	2447(29%)	40	17-73	8819(22%)	42	18-75
All cardiovascular events (n=6734)	1520(18%)	44	19-78	5214(13%)	46	20-79
Angina (n=2848)	634(8%)	42	18-74	2214(6%)	44	19-77
MI (n=2121)	445(5%)	42	18-75	1676(4%)	44	19-77
All cerebrovascular events (n=4007)	812(10%)	42	18-74	3195(8%)	43	19-77
Stroke (n=2368)	490(6%)	43	19-76	1878(5%)	44	19-77
TIA (n=1725)	367(4%)	42	18-74	1358(3%)	44	19-77
PVD (n=1291)	318(4%)	42	18-74	973(2%)	43	18-76

* median time to event is the median only for those who experience an event of interest and ignores censoring
IQR=inter-quartile range; MI= myocardial infarction; TIA= transient ischaemic attack; PVD= peripheral vascular disease

The frequency of development of all vascular events was higher in the gout group than in the control group for all types of vascular events.

The median time to event was also shorter in the gout group than the non-gout group for all vascular outcomes.

6.4 Survival Analysis

This section reports the results of the survival analysis. The results are presented by gender since there were statistically significant interactions between gout and gender in the models for many of the outcomes.

6.4.1 Unadjusted Analysis

Table 6.3 shows the results of the unadjusted Cox Proportional Hazards Regression. Absolute risk per 1000 person years for each outcome of interest is reported, alongside the hazard ratios (HRs) comparing the likelihood of having a first vascular event in patients with gout, compared to those without, before adjustment for known cardiovascular risk factors. The proportional hazards assumption for gout exposure was met for all types of vascular events. The results are presented by gender as there was a statistically significant interaction between gout and gender. The influence of follow-up time on the gout effect was found to be non-significant using Stata's own test of proportional hazards ($\chi^2_{(1)}$ =0.82 p=0.05).

Table 6.3: Unadjusted risk of a first vascular event between the gout and non-gout groups

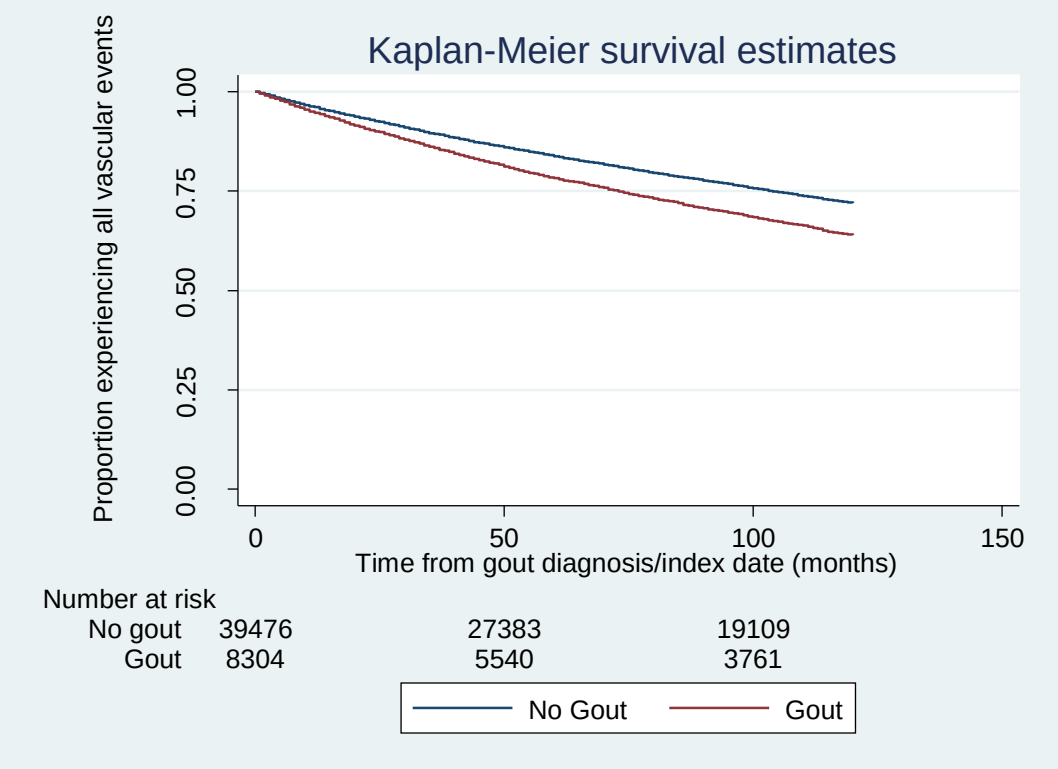
Outcome	Number of Events	**Men**			**Women**			**P for gender interaction**
		Gout	No Gout	Gout vs No Gout	Gout	No Gout	Gout vs No Gout	
		Absolute Risk per 1,000 person-years (95% CI)	Absolute Risk per 1,000 person-years (95% CI)	HR (95% CI)	Absolute Risk per 1,000 person-years (95% CI)	Absolute Risk per 1,000 person-years (95% CI	HR (95% CI)	
All vascular events	11,266	43.63 (41.55-45.77)	33.70 (32.86-34.55)	**1.29 (1.22-1.36)**	51.89 (48.32-55.64)	33.41 (32.15-34.71)	**1.56 (1.44-1.69)**	<0.01
All CHD	6734	28.46 (26.80-30.20)	21.06 (20.41-21.74)	**1.36 (1.27-1.45)**	29.11 (26.47-31.94)	17.72 (16.81-18.67)	**1.64 (1.48-1.82)**	<0.01
Angina	2848	11.80 (10.73-12.97)	8.95 (8.52-9.39)	**1.31 (1.18-1.46)**	12.32 (10.63-14.22)	7.23 (6.65-7.84)	**1.70 (1.45-2.00)**	<0.01
MI	2121	9.27 (8.34-10.29)	6.92 (6.55-7.31)	**1.33 (1.18-1.50)**	6.11 (4.93-7.48)	5.19 (4.70-5.72)	1.19 (0.95-1.49)	0.39
All CVD	4007	13.09 (11.98-14.28)	11.13 (10.66-11.63)	1.11 (0.97-1.26)	20.78 (18.55-23.19)	14.54 (13.72-15.41)	**1.39 (1.18-1.65)**	0.04
TIA	1725	6.04 (5.27-6.87)	4.77 (4.46-5.10)	**1.25 (1.09-1.45)**	9.34 (7.87-11.00)	6.06 (5.53-6.62)	**1.57 (1.30-1.89)**	0.07
CVA	2368	7.45 (6.62-8.38)	6.63 (6.26-7.02)	1.12 (0.98-1.27)	13.71 (11.92-15.09)	8.39 (7.77-9.05)	**1.67 (1.43-1.95)**	<0.01
PVD	1291	5.60 (4.88-6.41)	4.01 (3.72-4.31)	**1.39 (1.19-1.62)**	7.09 (5.81-8.55)	3.05 (2.68-3.46)	**2.35 (1.87-2.94)**	<0.01

HR=Hazard Ratio, CI=Confidence Interval, CHD= coronary heart disease, MI=Myocardial Infarction, CVD= Cerebrovascular Disease, TIA=Transient Ischaemic Attack, CVA=Cerebrovascular Attack, PVD=Peripheral Vascular Disease
Covariates include age at baseline, gender, gout*gender interaction

Table 6.3 shows there were statistically significant positive associations between gout and all the vascular outcomes with the exception of MI in the unadjusted analysis in women, and all outcomes except all cerebrovascular disease and CVA in men.

Figure 6.1 shows a Kaplan-Meier plot of the unadjusted results, which compared the likelihood of surviving without a vascular event between the gout and non-gout groups.

Figure 6.1: Kaplan-Meier plot of the likelihood of vascular event free survival between gout and non-gout participants.



There appears to be a clearly discernible difference in the proportion experiencing a vascular event between the two groups, starting almost immediately following

the index date, with this difference increasing over time from gout diagnosis or index date.

6.4.2 Adjusted Hazard Ratios

Table 6.4 presents the HRs comparing the risk of having a first vascular event after adjustment using Model 1(age at diagnosis of gout, or matched index date for controls, gender, gout*gender interaction, pre-index smoking, alcohol consumption, BMI, and Charlson Co-morbidity Index), and Model 2 (model 1 plus pre-index vascular risk factors hypertension, hyperlipidaemia, renal disease, aspirin and statin use) calculated using a Cox proportional hazard model. The results are presented by gender as there were statistically significant interactions between gout and gender in the models for many of the outcomes. The significance of the interaction in the gout effect between men and women, and the size of the difference are shown in Table 6.5.

Table 6.4: HRs comparing risk of vascular events between gout and non- gout groups after adjustment for confounders

Outcome	**Model 1**			**Model 2**		
	HR Men (95% CI)	HR Women (95% CI)	P for gender interaction	HR Men (95% CI)	HR Women (95% CI)	P for gender interaction
All vascular events	**1.22 (1.16-1.29)**	**1.45 (1.34-1.57)**	<0.001	**1.06 (1.01-1.12)**	**1.25 (1.15-1.35)**	<0.001
All CHD	**1.26 (1.18-1.35)**	**1.50 (1.35-1.67)**	0.005	**1.08 (1.01-1.15)**	**1.25 (1.12-1.39)**	0.024
Angina	**1.20 (1.08-1.34)**	**1.55 (1.32-1.82)**	0.010	1.02 (0.92-1.13)	**1.28 (1.09-1.51)**	0.003
MI	**1.30 (1.15-1.46)**	1.12 (0.89-1.40)	0.254	1.12 (1.00-1.27)	0.97 (0.77-1.22)	0.263
All CVD	1.11 (0.97-1.26)	**1.35 (1.14-1.60)**	0.068	0.95 (0.83-1.09)	1.17 (0.99-1.38)	0.058
TIA	**1.22 (1.05-1.41)**	**1.50 (1.24-1.81)**	0.085	1.02 (0.88-1.18)	**1.26 (1.05-1.53)**	0.796
CVA	1.08 (0.95-1.23)	**1.58 (1.35-1.84)**	<0.001	0.93 (0.81-1.06)	**1.34 (1.15-1.57)**	<0.001
PVD	**1.35 (1.16-1.58)**	**2.17 (1.73-2.73)**	<0.001	**1.18 (1.01-1.38)**	**1.89 (1.50-2.38)**	0.040

HR=Hazard Ratio, CI=Confidence Interval, CHD= coronary heart disease, MI=Myocardial Infarction, TIA=Transient Ischaemic Attack, CVA=Cerebrovascular Attack, CVD= cerebrovascular disease, PVD= peripheral vascular disease

Model 1 covariates: gender, gender*gout interaction, baseline age, body mass index >25kg/m^2, ever/never smoking, ever/never alcohol consumption, Charlson Co-morbidity Score

Model 2 covariates include Model 1 and baseline history of hypertension, hyperlipidaemia, chronic kidney disease, ever/never statin use, ever/never aspirin use

As reported in table 6.4, results for the male participants showed gout to be a risk factor for all forms of vascular events, with the exception of all cerebrovascular event and CVA. After adjustment in model 2, a statistically significant excess risk of all vascular events, all CHD, and PVD remained.

Results for the female participants found gout to be a risk factor for all forms of vascular events with the exception of MI after adjustment in model 1. After adjustment in model 2, risks remained significant but attenuated for all vascular events except MI and all cerebrovascular events.

Excess risk of all types of vascular events is greater in female than male participants. In model 1 the excess risk in women is approximately double that in men (with the exception of MI where there is significant risk in men but not women). After adjustment for the wider range of risk factors in model 2 this difference in risk increases to between three and four times the risk in women compared to men.

The magnitude and significance of the gout*gender interaction terms are shown in table 6.5 below.

Table 6.5: The significance and magnitude of the interaction in the gout effect between men and women

Outcome	**Model 1**			**Model 2**		
	Gender Interaction HR	95% CI	P for gender interaction	Gender Interaction HR	95% CI	P for gender interaction
All vascular events	**1.19**	**1.08-1.30**	<0.001	**1.17**	**1.07-1.29**	**0.001**
All cardiovascular events	**1.19**	**1.05-1.35**	0.005	**1.15**	**1.02-1.31**	**0.024**
Angina	**1.29**	**1.06-1.56**	0.010	**1.26**	**1.04-1.53**	**0.003**
MI	0.86	0.67-1.11	0.254	0.86	0.67-1.12	0.263
All cerebrovascular events	1.22	0.99-1.51	0.068	1.23	0.99-1.52	0.058
TIA	1.23	0.97-1.56	0.085	1.24	0.98-1.57	0.796
CVA	**1.45**	**1.19-1.78**	<0.001	**1.44**	**1.18-1.77**	**<0.001**
Peripheral vascular	**1.60**	**1.22-2.11**	<0.001	**1.60**	**1.22-2.12**	**0.040**

HR=Hazard Ratio, CI=Confidence Interval, MI=Myocardial Infarction, TIA=Transient Ischaemic Attack, CVA=Cerebrovascular Attack
Model 1 covariates age at diagnosis of gout/matched index date, gender, gout*interaction, body mass index >25kg/m^2, ever/never smoking, ever/never alcohol consumption, Charlson Co-morbidity Score
Model 2 covariates include Model 1 and history of hypertension, hyperlipidaemia, renal disease, ever/never statin use, ever/never aspirin use

The assumption of proportional hazards was tested for each model using Schoenfeld residuals. The covariates which did not satisfy proportional hazards assumptions and which were therefore entered as time-varying covariates were different for each vascular disease of interest. These are shown in table 6.6 below.

Table 6.6: Time-varying covariates entered into each Cox Regression model

	All vascular events		All CHD		Angina		MI		All CVD		TIA		CVA		PVD	
	M1	M2	M1	M2	M1	M2	M1	M2	M1	M2	M1	M2	M1	M2	M1	M2
Age at gout diagnosis	√								√							
Gender																
BMI >25						√								√		
Ever drinker	√	√	√		√		√		√		√	√	√			
Ever smoker							√	√					√			√
Charlson score														√		
Pre-index HTN		√		√		√		√								√
Pre-index HLD														√		
Pre-index renal disease																
Ever aspirin		√		√		√		√		√				√		√
Ever statin		√		√		√		√		√		√		√		√

BMI = body mass index; CHD = coronary heart disease; CVD = cerebrovascular disease; CVA = cerebrovascular disease; HLD = hyperlipidaemia; HTN = hypertension; PVD = peripheral vascular disease; TIA = transient ischaemic attack;
Model 1 (M1) = gender gout*gender interaction, baseline age, BMI, ever/never smoking, ever/never alcohol consumption, Charlson co-morbidity score
Model 2 (M2) = Model 1 plus baseline history of hypertension, hyperlipidaemia, renal disease, prescription of aspirin or statins

6.4.3 Results of Cox regression with follow-up censored at 1, 2 and 5 years

The relationship of time following diagnosis of gout with risk of vascular events was investigated by limiting follow-up to one, two and five years following diagnosis of gout (or matched index date), and risk of vascular events estimated during these time periods. As described in section 5.7 this was done to add clinical utility to the estimate of risk, to highlight trends or peaks in risk at different times following diagnosis of gout in order to inform decisions about optimum time for screening for and management of vascular risk.

The influence of follow-up time on the gout effect was examined by stratification within mutually exclusive time-intervals (first year, second year, years 2-5, and years 6-10) and testing for an interaction with time using the likelihood ratio test. The STATA LINCOM post-estimation command was then used to calculate the stratified effect size. These results are shown in Table 6.7

Table 6.7 The significance and magnitude of the interaction in the gout effect and follow-up time

Follow-up time (mutually exclusive)	HR	CI	p for Gout*Time interaction
Up to 1 year	1.29	0.90-1.85	0.55
1-2 years	1.26	1.02-1.56	0.40
2-5 years	1.42	1.20-1.67	0.75
5-10 years	1.36	1.30-1.43	0.58
HR = Hazard Ratio; CI=Confidence Interval			

There was no significant interaction between the gout effect and follow-up time as demonstrated by the likelihood ratio test (LR $\chi^2_{(4)}$ =1.12 p=0.89). The stability of the gout effect size over time was reinforced by the estat phtest (test of proportional hazards) which confirmed no effect of time ($\chi^2_{(1)}$ =0.82 p=0.05).

Table 6.8 shows the results comparing gout and non-gout participants risk of developing all vascular events limited to one year, two years, five years and ten years after index date, with and without adjusting for potential confounders.

Table 6.8: HRs comparing risk of developing all vascular events within a specified time following index date

Follow up time (Total person-years of follow-up)	Total number of events	Unadjusted		Model 1		Model 2	
		Men	Women	Men	Women	Men	Women
		HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI
Up to 1yr (27,394)	1953	**1.21 1.08-1.37**	**1.31 1.10-1.54**	**1.16 1.02-1.31**	**1.25 1.06-1.49**	1.02 0.90-1.16	1.12 0.94-1.32
Up to 2yrs (69,500)	3548	**1.13 1.03-1.24**	**1.38 1.21-1.57**	1.06 0.97-1.17	**1.33 1.16-1.51**	0.97 0.88-1.07	**1.21 1.07-1.38**
Up to 5yrs (387,638)	7308	**1.26 1.18-1.34**	**1.28 1.17-1.41**	**1.12 1.01-1.26**	**1.16 1.02-1.32**	0.97 0.87-1.08	1.04 0.91-1.18
Up to 10yrs (3,302,692)	11266	**1.29 1.22-1.36**	**1.56 1.44-1.69**	**1.22 1.16-1.29**	**1.45 1.34-1.57**	**1.06 1.01-1.12**	**1.25 1.15-1.35**
HR = hazard ratio; CI = confidence interval							

All vascular events

Excess risk of all vascular events was found in gout patients of both genders at 1, 2, 5 and 10 years post-diagnosis of gout in unadjusted analyses. As a general trend, excess risk rose with increasing duration of follow-up, although the magnitude of the increase between one and ten years post-diagnosis was greater in women with gout (25%) compared with men with gout (10%).

Risk of all vascular events is greater in women at one, two, five and 10 years following diagnosis of gout than in men. At one year post-diagnosis, in unadjusted analysis risk in women with gout is approximately 10% greater than that in men with gout and 30% higher than women without gout. The magnitude of this risk is attenuated after adjustment for the covariates in model 1, but remains significant in women at all time points, however significance is lost for men at two years of follow-up in men. After adjustment for the covariates in model 2 risk is further attenuated and only remains significant in women at 2 and 10 years of follow-up, and after 10 years of follow-up in men.

Both genders show an increase in risk with increasing duration of follow up, although the magnitude of this increase is much smaller in men (8% in unadjusted analysis, 6% after adjustment in model 1 and 4% in model 2) than women (25% in unadjusted analysis, 20% after adjustments in model 1 and 13% after adjustment in model 2)

Tables 6.9 and 6.10 show the unadjusted and adjusted results comparing gout and non-gout participants risk of all incident cardiovascular events, angina or MI with follow-up limited to one, two and five years.

Table 6.9: Unadjusted HRs comparing gout and non-gout participants risk of developing all CHD, angina or MI within a specified time following index date

Follow up time	All CHD			Angina			MI		
	No of events	Men	Women	No of events	Men	Women	No of events	Men	Women
		HR 95%CI	HR 95%CI		HR 95% CI	HR 95% CI		HR 95% CI	HR 95% CI
Up to 1yr	1084	**1.27 1.08-1.49**	**1.43 1.13-1.82**	493	**1.43 1.12-1.83**	1.43 1.00-2.04	299	1.25 0.90-1.73	0.73 0.41-1.30
Up to 2yrs	2019	**1.18 1.04-1.33**	**1.44 1.20-1.72**	911	1.12 0.93-1.35	**1.46 1.11-1.91**	543	1.16 0.92-1.47	0.92 0.59-1.42
Up to 5yrs	4183	**1.34 1.24-1.45**	**1.36 1.20-1.55**	1865	**1.21 1.07-1.38**	**1.51 1.25-1.83**	1234	**1.33 1.14-1.54**	0.98 0.73-1.31
Up to 10yrs	6734	**1.36 1.27-1.45**	**1.64 1.48-1.82**	2848	**1.31 1.18-1.46**	**1.70 1.45-2.00**	2121	**1.33 1.18-1.50**	1.19 0.95-1.49
All CHD includes incident angina, MI and all other codes relating to incident coronary heart disease CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction									

Table 6.10 Adjusted HRs comparing risk of incident cardiovascular events, angina or MI within a specified time following index date

Follow up time	All CHD				Angina				MI			
	Men		Women		Men		Women		Men		Women	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI
Up to 1yr	**1.19 1.01-1.40**	1.00 0.85-1.19	**1.32 1.04-1.68**	1.13 0.88-1.45	**1.30 1.02-1.67**	1.10 0.85-1.42	1.28 0.90-1.83	1.08 0.74-1.56	1.21 0.87-1.68	1.10 0.78-1.55	0.70 0.39-1.26	0.66 0.36-1.22
Up to 2yrs	1.08 0.95-1.22	0.96 0.85-1.09	**1.37 1.14-1.64**	**1.23 1.03-1.48**	1.01 0.83-1.22	0.91 0.75-1.11	**1.36 1.03-1.79**	1.23 0.93-1.62	1.10 0.87-1.40	1.07 0.84-1.36	0.88 0.57-1.37	0.80 0.51-1.26
Up to 5yrs	**1.20 1.11-1.30**	0.96 0.83-1.10	**1.24 1.08-1.41**	1.00 0.84-1.19	1.07 0.94-1.22	0.94 0.83-1.07	**1.36 1.12-1.65**	**1.29 1.06-1.57**	**1.27 1.09-1.49**	1.15 0.99-1.34	0.91 0.68-1.22	0.88 0.66-1.17
Up to 10yrs	**1.26 1.18-1.35**	**1.08 1.01-1.15**	**1.50 1.35-1.67**	**1.25 1.12-1.39**	**1.20 1.08-1.34**	1.02 0.92-1.13	**1.55 1.32-1.82**	**1.28 1.09-1.51**	**1.30 1.15-1.46**	1.12 1.00-1.27	1.12 0.89-1.40	0.97 0.77-1.22

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction

Model 1: Age at diagnosis of gout, gender, gout*gender interaction, BMI, ever/never smoking and alcohol exposure, Charlson co-morbidity index

Model 2: Model 1 plus preindex history of hypertension, hyperlipidaemia, chronic kidney disease, prescription of aspirin or statins

All CHD: Results of the unadjusted analyses showed both male and female participants with gout were at increased risk of all CHD events with the greatest excess risk in women. After adjustment in model 1 these risks persisted, although attenuated, but the trend differed between genders. In men, although there was an increased risk of all CHD after one and five years of follow-up, there was not after two years. After adjustment in model 2, men were only at increased risk of a cardiovascular event after 10 years of follow-up and women after two and ten years of follow-up.

Angina: Men were at increased risk of angina after one, five and 10 years, and women after two, five and 10 years in the unadjusted analysis. After adjustment in model 1, risks were attenuated but persisted at two, five and 10 years in women, and one and 10 years in men. After adjustment in model 2, risks were again attenuated but women were at increased risk of vascular event after five and 10 years of follow-up but men were not at any time point.

MI: Men were at increased risk of MI after five and 10 years of follow-up in the unadjusted analyses, after adjustment in model 1 these risks were slightly attenuated but persisted, but there was no increased risk of MI in men after adjustment in model 2. There was no statistically significant increased risk of MI in women at any time point in either the unadjusted or adjusted analysis.

Tables 6.11 and 6.12 show the results comparing gout and non-gout participants risk of developing all cerebrovascular events, TIA or CVA limited to one year, two years, five years and ten years after index date, with and without adjusting for potential confounders.

Table 6.11: Unadjusted HRs comparing gout and non-gout participants risk of developing all cerebrovascular events, TIA or CVA within a specified time following index date

Follow up time	All CVD			TIA			CVA		
	No of events	Men	Women	No of events	Men	Women	No of events	Men	Women
		HR 95%CI	HR 95%CI		HR 95% CI	HR 95% CI		HR 95% CI	HR 95% CI
Up to 1yr	647	1.01 0.78-1.30	1.34 1.00-1.78	233	1.13 0.75-1.71	1.49 0.95-2.34	310	0.88 0.60-1.29	1.32 0.87-2.00
Up to 2yrs	1170	0.99 0.82-1.19	**1.48 1.20-1.83**	443	0.94 0.69-1.28	**1.50 1.07-2.10**	555	0.96 0.73-1.26	**1.49 1.10-2.03**
Up to 5yrs	1569	1.12 1.00-1.27	1.17 1.00-1.37	1064	1.17 0.97-1.41	1.26 1.00-1.59	1356	1.06 0.89-1.25	**1.30 1.06-1.59**
Up to 10yrs	4007	1.11 0.97-1.26	**1.39 1.18-1.65**	1725	**1.25 1.09-1.45**	**1.57 1.30-1.89**	2368	1.12 0.98-1.27	**1.67 1.43-1.95**

All cerebrovascular disease (CVD) includes all incident TIA, CVA and all other codes relating to incident cerebrovascular disease

CVA = cerebrovascular accident; CVD = cerebrovascular disease; CI = confidence interval; HR = hazard ratio; TIA = transient ischaemic attack

Table 6.12: Adjusted HRs comparing risk of incident cerebrovascular events, TIA and CVA within a specified time following index date

Follow up time	All CVD				TIA				CVA			
	Men		Women		Men		Women		Men		Women	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI
Up to 1yr	0.99 0.76-1.27	0.94 0.72-1.22	**1.35 1.01-1.80**	1.22 0.90-1.64	1.11 0.73-1.68	1.02 0.67-1.54	1.50 0.96-2.36	1.26 0.78-2.05	0.83 0.57-1.22	1.05 0.81-1.36	1.30 0.86-1.98	1.19 0.78-1.82
Up to 2yrs	0.96 0.80-1.16	0.86 0.71-1.04	**1.46 1.18-1.80**	**1.39 1.13-1.71**	0.91 0.67-1.24	0.79 0.57-1.08	**1.46 1.04-2.06**	**1.43 1.02-2.01**	0.93 0.71-1.22	0.84 0.63-1.10	**1.46 1.07-2.00**	**1.45 1.06-1.98**
Up to 5yrs	1.07 0.95-1.21	0.93 0.83-1.06	1.13 0.96-1.32	1.08 0.92-1.26	1.11 0.92-1.34	0.95 0.78-1.15	1.22 0.96-1.54	1.17 0.93-1.49	1.01 0.85-1.20	0.88 0.74-1.05	1.23 1.00-1.51	1.17 0.95-1.43
Up to 10yrs	1.11 0.97-1.26	0.95 0.83-1.09	**1.35 1.14-1.60**	1.17 0.99-1.38	**1.22 1.05-1.41**	1.02 0.88-1.18	**1.50 1.24-1.81**	**1.26 1.05-1.53**	1.08 0.95-1.23	0.93 0.81-1.06	**1.58 1.35-1.84**	1**.34 1.15-1.57**

CVA = cerebrovascular accident; CVD = cerebrovascular disease; CI = confidence interval; HR = hazard ratio; TIA = transient ischaemic attack
Model 1: Age at diagnosis of gout, gender, gout*gender interaction, BMI, ever/never smoking and alcohol exposure, Charlson co-morbidity index
Model 2: Model 1 plus preindex history of hypertension, hyperlipidaemia, chronic kidney disease, prescription of aspirin or statins

All CVD: There was no increased risk of all cerebrovascular events in men in unadjusted analyses or adjusted analysis. Female participants with gout had an excess risk of all cerebrovascular events at two and ten years post-diagnosis of gout, but not at one and five years post-diagnosis. Excess risk was greatest at two years post-diagnosis in women, with an almost 50% increase in risk compared to female participants without gout. After adjustment in model 1, risks remained similar and were increased after one, two and 10 years of follow-up. After adjustment in model 2, only risk after two years of follow-up persisted.

TIA: Increased risk of TIA was only found after ten years follow-up male participants with gout in unadjusted analysis, and after adjustment in model 1, with no increased risk persisting after adjustment for the covariates in model 2. Women were found to be at increased risk of TIA when follow-up was limited to two and ten years in the unadjusted analysis, and this risk remained significant but attenuated after adjustment in both models 1 and 2. Risk of TIA was greatest when follow-up was limited to two years of follow-up.

No increased risk of CVA was found in male participants with gout, compared to those without in the unadjusted or adjusted analysis, whilst women with gout were found to have an increased risk of incident CVA at two, five and ten years after diagnosis of gout. This excess risk persists at both time points after adjustment for model 1 and 2, with risk remaining similar after adjustment in both models at the two year time point. Table 6.13 shows the results comparing gout and non-gout participants risk of incident peripheral vascular disease limited to one year, two years, five years and ten years after index date, with and without adjusting for potential confounders.

Table 6.13: HRs comparing risk of incident PVD within a specified time following index date

Follow up time	No. of events	Unadjusted		Model 1		Model 2	
		Men	Women	Men	Women	Men	Women
		HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI	HR 95%CI
Up to 1yr	191	1.44 1.00-2.08	**3.06** **1.58-5.92**	1.45 1.00-2.11	**2.96** **1.52-5.75**	1.33 0.92-1.93	**2.63** **1.35-5.13**
Up to 2yrs	368	**1.40** **1.07-1.83**	**2.17** **1.39-3.37**	**1.37** **1.05-1.80**	**2.12** **1.36-3.33**	1.25 0.95-1.64	**1.96** **1.24-3.09**
Up to 5yrs	815	**1.37** **1.13-1.66**	**1.98** **1.49-2.62**	**1.33** **1.10-1.62**	**1.79** **1.34-2.40**	1.20 0.99-1.46	**1.69** **1.26-2.25**
UP to 10yrs	1300	**1.39** **1.19-1.62**	**2.35** **1.87-2.94**	**1.35** **1.16-1.58**	**2.17** **1.73-2.73**	**1.18** **1.01-1.38**	**1.88** **1.50-2.38**

CI = confidence interval; HR = hazard ratio

Model 1: Age at diagnosis of gout, gender, gout*gender interaction, BMI, ever/never smoking and alcohol exposure, Charlson co-morbidity index

Model 2: Model 1 plus preindex history of hypertension, hyperlipidaemia, chronic kidney disease, prescription of aspirin or statins

Peripheral vascular disease

The excess risk of PVD was the highest of all risks identified. Men were at increased risk of PVD after two, five and ten years in the unadjusted analysis and after adjustment for the covariates in model 1, risk only persists after 10 years of follow-up in model 2. Women are at increased risk of PVD at all time points in unadjusted and after adjustment in model 1 and 2. Women are at greater risk than men, and risk is greatest after one year of follow-up.

The assumption of proportional hazards was tested using Schoenfeld residuals. Where this assumption was not satisfied, suggesting that risk associated with some or all covariates within the model did not remain constant over time, these covariates were re-entered into the model as time-covariates, allowing the assumption of proportional hazards to be satisfied for that particular vascular event of interest. The time-varying covariates entered into each model are shown in table 6.14 below.

Table 6.14: Time-varying covariates entered into each Cox Regression model by follow up time

Years post-diagnosis of gout	Model of adjustment	Age at diagnosis of gout	Gender	BMI >25	Ever drinker	Ever smoker	Charlson Score	Pre-index HTN	Pre-index HLD	Pre-index renal disease	Ever Aspirin	Ever Statin
1 year	M1			• Angina								
	M2			• Angina				• Angina				
2 years	M1			• All CVD								
	M2			• All vasc • All CVD				• All vasc • All CHD				• All vasc
5years	M1	• All vasc • All CHD • Angina • All CVD		• All CVD • CVA	• All vasc • All CHD • Angina	• All CVD • CVA						
	M2			• All vasc • All CVD • CVA		• All CVD • CVA		• All vasc • All CHD • Angina		• All CHD • All CVD	• Angina	• All vasc • All CHD • Angina • All CVD • TIA • CVA

Model 1 (M1) covariates = gender, gout*gender interaction, baseline age, BMI, ever/never smoking and alcohol exposure, Charlson co-morbidity index score
Model 2 (M2) covariates = Model 1 plus baseline history of hypertension, hyperlipidaemia, chronic kidney disease, prescription of aspirin or statins
BMI = body mass index; CHD = cardiovascular disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; HLD = hyperlipidaemia; HTN = hypertension

6.4.4 Multilevel discrete time event history analysis

This section reports the results of the discrete time event history analysis (MDtEHA). The follow-up time for each participant was divided into one-year time windows, starting from the index date, and ending at the vascular event, or the first of death, transfer away from the practice contributing the record, or censoring at ten years. The exposure status for each covariate within each of these one-year windows was determined by searching each participant's electronic health record (EHR). The results are presented in tables 6.15 and 6.16 as adjusted odds ratio of any participant (gout or no-gout) experiencing a vascular event associated with the covariates of interest.

Table 6.15: Odds ratio of all vascular events

Covariate	Odds ratio	95% CI	p for significance
Gout (in men)	1.37	1.34-1.42	<0.01
Gout (in women*)	1.56	1.50-1.63	<0.01
Age	1.03	1.03-1.03	<0.01
Gender	0.79	0.77-0.80	<0.01
Gout*Gender Interaction	1.13	1.08-1.20	<0.01
*Due to the significant gout*gender interaction the effect of gout in women on risk of vascular event was estimated using the lincom option			

Odds of vascular event reduced with each successive year following diagnosis of gout, from OR 0.89 (0.86-0.92) in the second year following baseline (as year 1 was the referent value) to OR 0.11 (0.10-0.12) in the tenth year. These are the

odds for all participants of experiencing an incident vascular event in each year, assuming that they have not experienced the event of interest prior to this, thus both those with and without gout have an odds ratio of vascular event of 0.89 in year 2 compared with year 1. It should also be considered that this is censored data, and thus participants (gout or non-gout) can only continue to be at risk of an event provided that they have not been censored in the previous window. It is likely that both a healthy survivor effect (whereby those at greatest risk of vascular event experience the event earlier leaving only those at least risk of vascular event "at risk" in later time windows) and the removal of those who have already been censored from the "at risk" population in successive years will reduce risk in all participants, and does not necessarily contribute anything to the discussion of the association between gout and risk of vascular event. For this reason these values will not be reported in models results of MDtEHA that follow.

The Hosmer & Lemeshow test of goodness-of-fit $p < 0.01$, indicates a significant difference between observed and expected number of events predicted by this model. This implies there are additional important predictors not included in this model, justifying further multivariable analysis, reported in table 6.16.

Table 6.16: Odds ratio of all vascular events according to exposure to all covariates during follow-up

Covariate	Odds ratio	95% CI	p for significance
Gout (in men)	1.16	1.12-1.21	<0.01
Gout (in women*)	1.25	1.19-1.32	<0.01
Male gender	0.79	0.77-0.81	<0.01
Gout*Gender Interaction	1.08	1.02-1.14	<0.01
Age in 1-yr window	1.03	1.03-1.03	<0.01
Incident hyperlipidaemia	1.13	1.09-1.18	<0.01
Incident CKD	0.66	0.61-0.72	<0.01
Charlson Score	1.22	1.20-1.23	<0.01
Blood pressure (Normal (≤150/90) referent)			
High (>150/90)	1.11	1.04-1.19	<0.01
Not recorded	0.71	0.67-0.76	<0.01
Body mass index (≤25 referent)			
>25	1.09	1.02-1.16	0.01
Not recorded	0.59	0.56-0.62	<0.01
Prescription of aspirin	2.61	2.53-2.69	<0.01
Prescription of statins	1.48	1.41-1.56	<0.01
*Due to the significant gout*gender interaction the effect of gout in women on risk of vascular event was estimated using the lincom option; CKD = chronic kidney disease			

Hosmer & Lemeshow test of goodness-of-fit p=0.33, indicates a reasonable model fit for the multivariable model.

There was a significant interaction between gout and gender as in the continuous model, and both women with gout and men with gout were more likely to experience an incident vascular event, and the effect of gout on likelihood of vascular event was greater in women.

Increased odds of experiencing a vascular event was predicted by increasing age, high blood pressure measurement in that year, raised BMI measurement in that year (BMI >25), hyperlipidaemia, increasing Charlson co-morbidity score, and prescription of statins and aspirin.

Reduced odds of experiencing a vascular event was predicted by male gender, renal disease and in those patients who did not have the blood pressure or BMI measured in that year.

6.5 Strengths and limitations of this study

The strengths and limitations of this analysis will be discussed alongside those of the sub-group analysis in chapter 7, as the main strengths and weaknesses are similar.

6.6 Summary

These results showed gout patients are at increased risk of all vascular events. This risk was highest in women, who are at increased risk of all vascular events: including all cardiovascular events, angina, CVA, TIA and PVD, whereas men are at increased risk of all vascular events, all cardiovascular events and PVD after adjustment for traditional vascular risk factors. A gender difference in the time at which risk of various vascular diseases is greatest was also identified and possible mechanisms discussed. MDtEHA was used to investigate population risk factors which influence the probability of experiencing a vascular event. These included gout in both men and women, and raised blood pressure and BMI, whilst male participants and those with CKD were less likely to experience a vascular event.

However, the factors which influence probability of incident vascular event in patients with gout remain unclear, and these will be investigated in further in Chapter 7.

Chapter 7: Gout group only analysis: methods and results

7.1 Overview

Having presented evidence of an association between gout and vascular disease in sections 3.8 and 6.4, and the risk factors which influence the risk of experiencing a first vascular event across all participants (gout and non-gout) in section 6.4.4, this chapter will investigate the factors which influence the risk of vascular event specifically in patients with gout, focussing especially in the role of uric acid and treatment for hyperuricaemia as discussed in section 2.5.

7.2 Gout-specific risk factors and risk of vascular event

In order to try to understand why some patients with gout experience a vascular event whilst others do not, a subgroup analysis of the gout patients was undertaken.

The influence of the known vascular risk factors included in the multivariable analysis of the cohort study discussed above on the risk of experiencing a vascular event were investigated, but additional gout-specific characteristics were also investigated. These were:

- Allopurinol prescription (the most commonly used urate lowering therapy): yes/no
- Hyperuricaemia (defined as SUA > 360 micromol/litre) within the 6 months before and after diagnosis of gout, and during follow-up (using an average value generated for each participant between baseline and vascular event or censoring): yes/no/missing

- Frequency of consultation for gout between diagnosis of gout and event of interest or censoring (divided into quartiles), as a proxy for gout severity
- Total consultations prior to event of interest or censoring (divided into quartiles), as a proxy for consulting behaviour

7.2.1 Statistical methods

Logistic regression uses either continuous (e.g. weight in kilograms) or categorical predictor variables (e.g. body mass index 17-20, 21-25, 26+) to predict the odds of a binary (e.g. presence or absence of a vascular event) or ordinal (e.g. mild, moderate or severe disease) outcome variable, in this case the odds of a participant with gout experiencing an incident vascular event using a combination of predictor variables specific to patients with gout.

The odds predicted using logistic regression can be considered to be the probability of the participant experiencing a vascular event divided by the probability of not experiencing a vascular event. This probability will always fall between 0 and 1, resulting in an easier interpretation of results. This probability also takes into account the threshold effect, whereby the collective effect of a group of variables on an individual's risk of an outcome is low until a particular threshold is reached, after which risk rises rapidly, remaining around 1 once the level of those collective variables is high enough. The S-shaped curve of the logistic function used to predict outcome from variables in this model (rather than the straight line used in linear regression) represents this threshold effect well. (Kleinbaum & Klein, 2010) The natural logarithm of the odds is then taken to allow "transformation" of the binary outcome to become continuous, and the log-odds are then fitted against the predictor variables using linear regression. The inverse

value of the predicted value of the log-odds is then taken, and this becomes the odds ratio of experiencing the event of interest based upon the predictors entered into the model. (Kleinbaum & Klein, 2010)

The covariates entered into the model were the known vascular risk factors included in the main cohort study analysis above, a binary indicator for ever/never having been prescribed allopurinol, a categorical variable for yes/no/missing hyperuricaemia in the 6 months before and after diagnosis of gout, and between diagnosis and date of vascular event or censoring, and a categorical variable for frequency of consultations. Frequency of consultations (for gout and total consultations) was categorised into quartiles (with the lowest quartile as the referent category) as the numbers of consultations varied significantly and so to include this as inclusion as a continuous variable would have yielded an odds ratio per unit increase in number of consultations that was too small to be of practical value.

Goodness-of-fit of the model (i.e. how well the model predicts the outcome variable from the predictors) was assessed using the Hosmer & Lemeshow test of model fit. This test compares observed with expected frequency of outcomes using a Pearson chi-squared test. The observed and predicted frequency should match closely, and the closer the match, the better the model fit, indicated by a non-significant p value associated with the chi squared test. (Hosmer et al, 2013)

7.3 Medication and risk of vascular event

Other factors which may increase or reduce risk of vascular event include prescription medication. Exposure to certain medications, such as anti-platelet (e.g. aspirin) and cholesterol-lowering (e.g. HMG Co-A Reductase inhibitors “statins”) medications, may confer protection against vascular disease, (Antithrombotic Trialists' Collaboration, 1994; Antithrombotic Trialists' Collaboration, 2002; Naci et al, 2013) whereas exposure to others, such as non-steroidal anti-inflammatory drugs, may increase risk of vascular events. (Bhala et al, 2013)

Multilevel discrete time event history analysis (MDtEHA) was used to explore the effect of medications used to treat both acute and chronic gout, and to treat co-morbidities which may predispose to vascular disease (e.g. hypertension, hyperlipidaemia) or in primary prevention of vascular disease (e.g. antiplatelet medications) on likelihood of incident vascular event in patients with gout.

Medications of interest were:

- Treatments for acute gout
    - Colchicine
    - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Treatments for chronic gout
    - Allopurinol
    - Uricosurics e.g. probenecid

- Anti-hypertensives
    - Angiotensin-converting enzyme (ACE) inhibitors
    - Angiotensin II receptor antagonists (AII)
    - Beta-adrenergic receptor antagonists
    - Calcium channel antagonists
    - Centrally acting antihypertensives
    - Diuretics
    - Renin inhibitors
    - Vasodilators
- Anti-platelet medications
    - Aspirin
    - Clopidogrel
    - Dipyridamole
- Lipid-lowering medications
    - Hydroxymethylglutaryl-CoA reductase (HMG-CoA) inhibitors
    - Fibrates
    - Cholesterol-absorption inhibitors

The rationale for these choices is described below.

7.3.1 Treatments for acute gout

Treatments for acute gout are aimed at reducing the MSU-crystal associated inflammation which results in the painful synovitis which separates clinical gout from asymptomatic hyperuricaemia. Since this inflammation has been implicated in the link between gout and vascular disease, it would seem reasonable to examine the effect of treatments used to reduce inflammation on the risk of vascular disease in patients with gout.

Colchicine

As described in Chapter 1, colchicine is a commonly prescribed treatment for acute gout that works by inhibiting neutrophil motility and activity. Since activated neutrophils have been identified in atherosclerotic plaques in patients with unstable coronary disease, it has been suggested that inhibition of these activated neutrophils using colchicine may reduce risk of vascular events. Existing literature has examined the effect of colchicine on risk of vascular events in patients with existing vascular disease, demonstrating effective secondary prevention of cardiovascular events in those with existing stable coronary disease. (Nidorf et al, 2013) The effect of colchicine on the risk of cardiovascular disease in patients with gout has also been explored, but the primary outcome for the majority of patients included in this study is limited to myocardial infarction, and the available evidence is conflicting. Grimaldi-Bensouda et al, 2013, found no effect on risk of MI associated with use of colchicine, whereas Crittenden et al, 2012, reported decreased prevalence of myocardial infarction in patients with gout treated with colchicine, but did not examine other vascular outcomes. (Crittenden et al, 2012; Grimaldi-Bensouda et al, 2014) Thus the effect of colchicine on vascular outcomes in patients with gout merits further investigation.

NSAIDs

NSAIDs are commonly used treatments for acute gout, and yet use of NSAIDs has been associated with increased risk of vascular event. (Bhala et al, 2013) A meta-analysis of 754 trials reported use of either selective COX-2 inhibitors or diclofenac to increase risk of vascular death by half, risk of major vascular event by a third,

and risk of major coronary event by almost two thirds. Ibuprofen was shown to double the risk of major coronary events, and all NSAIDs to double the risk of heart failure. (Bhala et al, 2013) In light of the association of both NSAIDs and gout with increased risk of vascular event, the relationship of prescription NSAID use in gout patients with their risk of incident vascular disease merits further examination, as there is little existing literature, although NSAIDs purchased over-the-counter cannot be accounted for and needs to be considered as a potential limitation which may affect the results.

7.3.2 Treatments for chronic gout

Since hyperuricaemia has been established as a risk factor for both cardiovascular and cerebrovascular disease it would seem likely that reduction of serum uric acid (SUA) level using urate lowering therapy would also impact on the risk of cardiovascular and cerebrovascular events. (Kim et al, 2009; Kim et al, 2010) Drugs in common usage at the time the study data was collected included xanthine oxidase inhibitors (e.g. allopurinol) and uricosurics (e.g. probenecid). Febuxostat (an alternative xanthine oxidase inhibitor) was not approved for use until 2008, and so would not have been in use during our study period (incident diagnosis of gout between 1987 and 1999, with a maximum of 10 years follow-up), and was therefore not included in this investigation.

Allopurinol

Allopurinol is the most commonly used urate lowering therapy prescribed for the treatment of chronic gout. (Annemans et al, 2008; Soriano et al, 2011) Evidence

supports various cardiovascular benefits conferred by allopurinol in non-gout patients, including reduction in blood pressure, (Agarwal et al, 2013) and left ventricular mass in patients with left ventricular hypertrophy and diabetes or ischaemic heart disease, (Rekhraj et al, 2013; Szwejkowski et al, 2013) and an increase in exercise tolerance in patients with chronic stable angina. (Noman et al, 2010) However, little is known of the effect of allopurinol on vascular risk in patients with gout.

Uricosurics

There is little evidence investigating the effect of uricosurics on vascular risk in either gout or non-gout patients, but it would not be unreasonable to consider the impact of other forms of urate lowering therapy on vascular risk in addition to xanthine oxidase inhibitors. Since uricosurics lower serum urate levels using a different mechanism to xanthine oxidase inhibitors, by blocking renal tubular reabsorption of uric acid thus increasing renal excretion of urate, examination of the prescription of uricosurics on risk of vascular disease in gout may suggest whether any effect of urate-lowering therapy on vascular disease relates directly to the reduction in serum urate levels, or to the mechanism by which that urate lowering therapy works.

7.3.3 Medications used to treat cardiovascular risk factors

In patients at risk of vascular disease several groups of medications are typically used to try to reduce that risk, either as primary prevention before the disease is manifest, or secondary prevention to prevent further progression of disease.

These medicines are usually those which treat co-morbidities which predispose to vascular disease (e.g. hyperlipidaemia or hypertension) or target some of the mechanisms which underlie the pathogenesis of vascular disease (e.g. anti-platelet medications). These are discussed below.

Anti-platelet medication

Since platelets are known to play an important role in the pathogenesis of coronary artery diseases, anti-platelet medications have become commonplace in both the primary and secondary prevention of vascular disease. (Clappers et al, 2007) Currently available anti-platelet medication used in the prophylaxis of various forms of vascular disease includes aspirin, clopidogrel and dipyridamole. Each acts on a different part of the thrombotic pathway, and for this reason may also be used in combination, particularly in cerebrovascular disease or post-MI. (Jones et al, 2013; National Collaborating Centre for Chronic Conditions, 2008a)

Aspirin has been shown to reduce risk of serious vascular events (non-fatal MI, non-fatal stroke, or vascular death), arterial occlusion and venous thromboembolism among patients at high risk. (Antithrombotic Trialists' Collaboration, 1994; Antithrombotic Trialists' Collaboration, 2002) It does this primarily through actions which are anti-inflammatory, protect from oxidative stress, enhance fibrinolysis, and suppress plasma coagulation and platelet-dependent inhibition of thrombin production. (Mehta, 2002; Patrono, 1994)

Salicylates are also known to exert a uricosuric effect in high doses. However, in low doses such as those commonly used for cardiovascular protection, aspirin is

thought to increase levels of urate by reducing renal excretion. (Caspi et al, 2000) Thus the effect of aspirin on risk of vascular disease in gout may be conflicting in that it may have an anti-platelet effect, but also increase uric acid.

Other anti-platelet drugs used to reduce risk of vascular diseases include clopidogrel which is used in the prophylaxis of coronary artery disease, and dipyridamole which is used in the prophylaxis of cerebrovascular disease. Due to the increased cost when compared with aspirin, clopidogrel and dipyridamole are less frequently used in mono-therapy.

Cholesterol-lowering medications

Hypercholesterolaemia is a common comorbidity in patients with gout and is reported to be present in approximately 45% of gout patients. (Annemans et al, 2008; Riedel et al, 2004) The cholesterol-lowering class of drugs include statins, fibrates and ezetimibe. Statins and fibrates reduce lipid levels by inhibiting the body's production of cholesterol and triglycerides by the liver, whilst ezetimibe inhibits intestinal absorption of dietary cholesterol.

Given the association between hyperlipidaemia and atherosclerotic vascular disease, and the reduction in all-cause mortality, cardiovascular mortality and major coronary events attributed to these drugs, it would seem reasonable to investigate their effect on risk of vascular disease in patients with gout. (Naci et al, 2013)

Anti-hypertensives

Aside from the effect of controlling hypertension on vascular risk, use of antihypertensives may influence risk of vascular disease through the more direct action of some on levels of SUA.

ACE inhibitors (particularly enalapril and captopril), angiotensin II receptor antagonists (particularly losartan), calcium channel blockers such as verapamil, and beta-blockers (particularly timolol) are also known to have a uricosuric action. (Spieker et al, 2002)

Thus, the inclusion of all classes of anti-hypertensive drugs in this investigation of their effect on risk of vascular disease in gout patients may provide a helpful comparison between the effect of those thought to be uricosuric, and those that are not.

Diuretics are a particular class of antihypertensive known to have a long standing association with gout as chronic diuretic therapy is known to predispose to hyperuricaemia. A number of mechanisms have been proposed to explain this, including increased uric acid reabsorption resulting from reduction in circulating volume and direct effects on the urate transporters in the proximal tubule, and competitive inhibition of organic anion transporter (OAT) 4 by diuretics increasing urate reabsorption has also been shown. (Hagos et al, 2007; Hueskes et al., 2012) Some diuretics have also been shown to reduce uric acid excretion. (El-Sheikh et al, 2008)

Since the main therapeutic indications for diuretics are the treatment of fluid retention associated with cardiovascular diseases such as heart failure and hypertension, it may be that the effect of diuretics is to reduce risk of vascular disease in patients with gout through reducing risk factors such as hypertension. However, since diuretics predispose to hyperuricaemia, and hyperuricaemia is known to predispose to vascular disease, (Kim et al, 2009; Kim et al, 2010) it may be that diuretics increase risk of vascular disease in patients with gout by reducing urate excretion and driving up SUA levels.

7.3.4 Calculation of dosage

Medications of interest were identified from each participant's electronic health records (EHR) using codes returned by a browser provided by the CPRD. Each code uniquely identified a particular strength of tablet, and this could be combined with the quantity of tablets supplied and duration of prescription, or the number of tablets the patient was directed to take per day, to identify not only the presence or absence of a prescription for that medication in each year-long time window, but to calculate the prescribed dosage.

For the purpose of analysis, dosage of treatment was converted into defined daily dose (DDD). This is a validated measure of drug consumption maintained and administered by the World Health Organisation (WHO), and is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. (http://www.whocc.no/ddd/definition_and_general_considera/, last accessed 19th June 2014) The DDD of each drug is considered to be

functionally equivalent to that of any other drug used for a similar purpose, and thus can be used to compare drugs within and across pharmacological groups, facilitating our comparison of the effect of groups of drugs (treatments for acute and chronic gout and cardioprotective medications) on risk of vascular disease.

It is calculated by multiplying the dose of the drug prescribed by the quantity given and dividing this by the DDD value assigned to that particular drug. Total dose of drugs (reported as DDDs) prescribed in each year-long time window were calculated for each participant, and then divided by 365 to give an average DDD dose per day. This average was then categorised into quartiles based on the use by pharmacological group.

Since allopurinol, once prescribed, is likely to remain a lifelong prescription in the absence of adverse events or intolerance, it is usually added to the patients repeat prescription. This allows the patient to request an allopurinol prescription without needing a repeat consultation. However, repeat prescriptions are only usually issued if they have been requested by, or on behalf of, the patient. Since allopurinol has limited indications, patients are only likely to continue to request repeat issues if they are actually taking the tablets. Therefore, non-compliance can be identified by periods where allopurinol is not issued following initiation. The number of prescriptions for allopurinol issued following initiation throughout remaining follow-up may provide supporting evidence of compliance or non-compliance in this sample. The effect on risk of incident vascular event of either compliance or non-compliance with allopurinol, as well as the dose prescribed, in each time window was examined using MDtEHA. Since comparison within or

between other pharmacological groups was not required, dosage was divided into <300mg, =300mg (the most commonly prescribed fixed dosage) or >300mg per day, instead of using DDDs. Compliance with allopurinol was measured using medication possession ratio (MPR). (Sclar et al, 1991) This is the number of days of medication supplied within a set time interval divided by the number of days in the specified time interval and was calculated for each year long time window.

Known vascular risk factors which may influence the relationship between medications and risk of incident vascular event were identified from the patient's electronic record, in each one year time window, using codes identified from the CPRD browser. The rationale for selection of these criteria is described in detail in section 5.4.

Analysis was conducted using SPSS Statistics version 20.0 (SPSS Inc, IBM Corp; 2012) and Stata statistical software release 12 (StataCorp: College Station, TX, 2011)

7.4 Results

This section will report the results of the investigation of factors influencing the odds of a vascular event in patients with gout. The frequency and percentage of gout participants (n= 8386) who have ever been prescribed urate lowering therapy (allopurinol), have recorded hyperuricaemia at first diagnosis of gout, hyperuricaemia over follow-up (using the mean of any recorded urate measurements between diagnosis of gout and event of interest or censoring), and the distribution of the number of consultations for gout following diagnosis (as a proxy for severity), and total number of consultations (as a proxy for consulting

behaviour) will be presented. This will be followed by the results of the analysis of the influence of these risk factors on odds of an incident vascular event in patients with gout.

7.4.1 Gout case participants and gout-specific exposures

This section reports the frequency and percentage of gout participants who have the aforementioned gout-specific exposures.

Mean age at diagnosis with gout was 66.6 years (SD 10.8). 3527 (42%) participants were prescribed allopurinol prior to having a vascular event, with median time to prescription of allopurinol from diagnosis of gout being 10 months (interquartile range 5-54 months). Mean age at first prescription of allopurinol was 72.4 years. The most frequently prescribed dosage of allopurinol prescribed was 300mg (63.8%) with only (36.2%) prescribed a dosage other than 300mg and (1%) prescribed more than 300mg)

Routine measurement of SUA was not common practice. Only 46% (n=3871) of participants had any measurement of serum urate between 6 months prior to their diagnosis of gout and the end of their complete follow up. Less than 40% (n=1206) of the participants who were prescribed allopurinol as urate lowering therapy had a recorded measurement of SUA within the 6 months before or after commencing this treatment. The frequency and percentage of gout participants who have the exposures of interest are summarised in table 7.1 below.

Table 7.1 Frequency and percentage of gout-specific exposures

Gout specific exposures	Frequency (n=8386) (%)
Record of urate lowering therapy (allopurinol) prescription	
Yes	3527 (42.1)
No	4859 (57.9)
Abnormal presenting urate level (≥360 micromol/L)	
Yes	1296 (15.5)
No	299(3.6)
Missing	6791(81.0)
Abnormal mean urate level (≥360 micromol/L)	
Yes	2883 (34.4)
No	981(11.7)
Missing	4522 (53.9)
No of consultations for gout	
1	6653 (79.3)
2	1378 (16.4)
3	322 (3.8)
4+	33 (0.4)

7.4.2 Association of gout-specific exposures with subsequent vascular disease in gout cases

This section reports the association between gout-specific exposures and odds of experiencing an incident vascular event in gout patients.

Table 7.2 presents the odds of a vascular event according to gout-specific exposure, and shows that gout participants exposed to allopurinol were more likely to experience all vascular and cardiovascular events, whilst those consulting more frequently for gout were less likely to experience a vascular event.

Gout participants who did not have serum urate recorded at diagnosis of gout, or over their follow-up (until vascular event or censoring) were also more likely to experience vascular events, highlighting the role of surveillance in patients with gout in the management of vascular risk.

Table 7.2 Associations between gout-specific exposures and vascular event

	All vascular*	All CHD*	Angina*	MI*	All CVD*	TIA*	CVA*	PVD*
Ever/Never exposure to allopurinol prior to vascular event (Referent value: never exposed)								
Ever exposed to Allopurinol	**1.15 1.06-1.26**	**1.27 1.14-1.42**	**1.43 1.21-1.69**	1.13 0.92-1.39	1.00 0.86-1.17	1.09 0.87-1.36	0.96 0.79-1.16	1.15 0.91-1.47
Number of gout consultations (quartiles) (Referent value: quartile1)								
2	0.89 0.80-1.00	0.89 0.78-1.02	**0.80 0.65-0.99**	0.90 0.70-1.15	0.94 0.78-1.13	0.93 0.71-1.21	0.94 0.75-1.18	0.78 0.58-1.05
3	**0.78 0.68-0.89**	0.85 0.72-1.00	**0.71 0.55-0.92**	0.73 0.54-1.00	**0.64 0.50-0.82**	**0.56 0.39-0.82**	**0.61 0.44-0.83**	**0.56 0.38-0.83**
4	**0.62 0.55-0.69**	**0.63 0.54-0.72**	**0.42 0.34-0.53**	**0.57 0.43-0.74**	**0.61 0.50-0.74**	**0.55 0.41-0.74**	**0.59 0.46-0.77**	**0.48 0.35-0.65**
Total number of consultations (quartiles) (Referent value: quartile 1)								
2	1.03 0.84-1.27	1.00 0.76-1.32	1.36 0.81-2.29	1.05 0.69-1.60	1.06 0.74-1.51	0.88 0.47-1.65	1.15 0.75-1.77	2.26 1.00-5.10
3	1.06 0.87-1.28	1.07 0.83-1.38	1.60 0.98-2.59	0.80 0.54-1.20	1.19 0.86-1.65	1.54 0.89-2.66	1.02 0.68-1.53	**2.55 1.17-5.55**
4	**1.35 1.13-1.62**	**1.47 1.16-1.88**	**2.88 1.81-4.57**	0.83 0.56-1.21	1.29 0.94-1.77	**1.84 1.09-3.12**	0.99 0.67-1.46	**3.67 1.72-7.83**
Presenting hyperuricaemia (≥360 micromol/L) (Referent value: no)								
Yes	1.28 1.00-1.63	1.24 0.91-1.69	1.50 0.92-2.46	1.57 0.84-2.91	**1.78 1.11-2.87**	1.53 0.77-3.02	**1.85 1.02-3.34**	1.01 0.56-1.80
Missing	**1.29 1.02-1.62**	1.21 0.91-1.61	1.42 0.89-2.24	1.52 0.85-2.71	**1.76 1.12-2.74**	1.68 0.89-3.17	1.61 0.92-2.80	0.93 0.55-1.58
Mean urate level hyperuricaemic (≥360 micromol/L) (Referent value: no)								
Yes	**1.30 1.08-1.56**	**1.28 1.02-1.61**	0.95 0.64-1.40	1.17 0.68-2.02	1.27 0.96-1.69	1.10 0.75-1.63	1.30 0.82-2.06	0.93 0.58-1.48
Missing	**1.36 1.13-1.64**	**1.31 1.05-1.65**	**0.61 0.40-0.92**	1.13 0.65-1.97	**1.36 1.02-1.80**	1.02 0.69-1.50	**1.93 1.23-3.02**	0.94 0.60-1.48
Hosmer & Lemeshow p	0.36	0.16	0.87	0.11	0.62	0.56	0.54	0.68

* Odds ratio (95% Confidence intervals) are presented
CHD = coronary heart disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; PVD = peripheral vascular disease; TIA = transient ischaemic attack

7.4.3 Association between odds of experiencing a vascular event and exposure to medications used to treat acute and chronic gout

This section will present the results of the multilevel discrete-time event history analysis (MDtEHA) investigating how changing exposure to medications used to treat acute and chronic gout affect the odds of an incident vascular event. As previously discussed, the covariates of interest were measured in each year-long follow-up window from diagnosis of gout. The results presented are the odds of incident vascular event in all gout patients associated with exposure to each particular covariate following diagnosis of gout. Table 7.3 shows the odds ratio of experiencing an incident vascular event in patients with gout who are exposed to medications used to treat acute and chronic gout, in comparison with those who are not.

Table 7.3 Daily dose of treatments for gout and odds of all vascular events

	NSAIDs (n=5458)		Colchicine (n=850)		Allopurinol (n=3527)		Uricosurics (n=159)	
Number of events	1587		198		806		23	
Covariate	Odds ratio	95% CI	Odds ratio	95%CI	Odds ratio	95% CI	Odds ratio	95% CI
Average dose of drug (DDD) per day (quartiles) (reference category: no exposure)								
1	**1.18**	**1.08-1.28**	1.11	0.80-1.55	0.99	0.87-1.14	**3.68**	**1.82-7.44**
2	1.07	0.96-1.18	0.91	0.62-1.35	1.00	0.86-1.16	2.48	0.88-6.99
3	**1.31**	**1.18-1.46**	1.15	0.79-1.69	1.10	0.92-1.31	1.96	0.56-6.91
4	**1.35**	**1.17-1.55**	0.84	0.43-1.65	1.07	0.87-1.33	**3.98**	**1.12-14.12**
Age in 1-yr window	**1.03**	**1.02-1.04**	**1.03**	**1.02-1.04**	**1.03**	**1.02-1.04**	**1.03**	**1.02-1.04**
Male gender	**0.84**	**0.74-0.96**	**0.85**	**0.75-0.96**	**0.85**	**0.75-0.96**	**0.84**	**0.75-0.96**
Incident hyperlipidaemia	1.18	0.99-1.41	1.18	0.99-1.41	1.18	0.99-1.41	1.18	0.99-1.41
Incident CKD	0.78	0.58-1.04	0.77	0.58-1.02	0.76	0.57-1.01	0.75	0.57-1.00
Charlson Score	**1.20**	**1.14-1.26**	**1.19**	**1.14-1.25**	**1.20**	**1.14-1.26**	**1.19**	**1.14-1.25**
Blood pressure (Normal (≤150/90) referent)								
High (>150/90)	**1.29**	**1.19-1.40**	**1.30**	**1.20-1.40**	**1.29**	**1.20-1.40**	**1.29**	**1.20-1.40**
Not recorded	**0.79**	**0.73-0.86**	**0.79**	**0.73-0.85**	**0.79**	**0.73-0.86**	**0.79**	**0.73-0.85**
Body mass index (≤25 referent)								
>25	0.92	0.77-1.09	0.93	0.79-1.10	0.93	0.78-1.10	0.93	0.79-1.11
Not recorded	**0.75**	**0.64-0.86**	**0.75**	**0.65-0.87**	**0.75**	**0.65-0.87**	**0.75**	**0.65-0.88**
p for significance of test of goodness of fit*	0.07		0.07		0.07		0.07	

CI= confidence interval; DDD= defined daily dose; CKD = chronic kidney disease

*Used Hosmer & Lemeshow test for model fit where non-significant test indicates model approximates the data i.e. good model fit

As described in section 4.6.2, the discrete-time event history model has the advantage that covariates measured following diagnosis of gout can be included in the model (e.g. incidence of new co-morbidities, giving up smoking or prescription of new medication), as opposed to be measured at baseline as in Cox proportional hazards (CPH) regression. This results in an overall estimate of the odds of experiencing an incident vascular event in all gout patients associated with each covariate but taking into account changes in risk factors over the course of follow-up, rather than simply those present at baseline as in the Cox regression. The results presented in table 7.3 show the odds of experiencing an incident vascular event associated with each covariate across all gout patients.

An incident vascular event was found to be more likely in patients who had been exposed to prescribed NSAIDS with a trend in risk associated with increased exposure, and in those who were in the lowest and highest strata of exposure to uricosurics, although the numbers exposed to uricosurics was small. Likelihood of experiencing a first vascular event was no different in patients who had been exposed to colchicine or allopurinol than those who had not.

In addition, odds of experiencing a first vascular event was also increased by increasing age and Charlson score and a high blood pressure measurement recorded in that year.

In contrast, male patients, those with incident chronic kidney disease, and those in whom there was no recorded measurement of blood pressure or BMI in that year were less likely to experience a first vascular event.

Given that risk of vascular disease was unaffected by exposure to allopurinol at any dose strata, this relationship was explored further. Table 7.4 presents the

results where the influence of medication possession ratio (the proportion of each year long time window the patient had a prescription for allopurinol issued, and considered a proxy for compliance with allopurinol treatment) and mean daily dosage of allopurinol in milligrams (not defined daily doses as in table 7.3 as no comparison with other medication groups was planned for these results) per year-long time window were included as covariates to explore their influence on the risk of experiencing an incident vascular event.

Table 7.4 Dose and duration of allopurinol therapy in risk of all vascular events

Covariate	Odds ratio	95% CI	p for significance
MPR	**0.55**	**0.42-0.72**	<0.01
Mean allopurinol dosage in each year (referent no allopurinol)			
<300	**1.44**	**1.13-1.85**	<0.01
300	**1.57**	**1.23-2.01**	<0.01
>300	1.38	0.61-3.11	0.43
Male gender	0.96	0.86-1.07	0.47
Age in 1-yr window	**1.02**	**1.01-1.02**	<0.01
Incident hyperlipidaemia	**0.67**	**0.56-0.80**	<0.01
Incident CKD	**0.33**	**0.26-0.43**	<0.01
Charlson Score	**1.54**	**1.48 -1.61**	<0.01
Blood pressure (Normal (≤150/90) referent)			
High (>150/90)	**1.52**	**1.37-1.69**	<0.01
Not recorded	**0.75**	**0.67-0.85**	<0.01
Body mass index (≤25 referent)			
>25	0.84	0.69-1.02	0.08
Not recorded	**0.74**	**0.62-0.88**	<0.01
Prescription of aspirin	**5.46**	**4.90-6.09**	<0.01
Prescription of statins	**1.61**	**1.38-1.89**	<0.01
CI= confidence interval; CKD = chronic kidney disease; MPR=medication possession ratio			

Participants taking ≤300mg of allopurinol (300mg fixed dose being the most common way to prescribed allopurinol in primary care) were more likely to experience a first vascular event than those who had never taken allopurinol, but those taking >300mg were not, although only 36.2% of the study population were prescribed a dose other than 300mg, and of those only 1% were prescribed a dose greater than 300mg per day.

Increasing medication possession ratio (the proportion of each year-long time window that the patient has a prescription for allopurinol) was found to reduce the risk of experiencing an incident vascular event.

7.4.4 Association between exposure to medications used to treat vascular risk factors and risk of incident vascular event in patients with gout.

This section presents the results of the MDtEHA investigating how changing use of medications used to treat vascular risk factors affect the risk of experiencing an incident vascular event in patients with gout.

As before, the covariates of interest measured in each year following diagnosis of gout were used to estimate odds ratio of experiencing an incident vascular event in all gout patients associated with each particular covariate. The results presented are the likelihood of any gout patient experiencing an incident vascular event where that covariate is present (presence compared with absence, a one unit increase in value or progression between categories in categorical variables).

Table 7.5 shows the odd ratios in gout patients of experiencing an incident vascular event associated with exposure to medications used to reduce vascular risk.

Table 7.5: Daily dose of drugs used to treat vascular risk factors and odds of all vascular events

	Anti-hypertensives (n=5563)		Anti-platelet drugs (n=1979)		Lipid-lowering (n=1376)	
Number of events	1987		1002		483	
Covariate	Odds ratio	95% CI	Odds ratio	95%CI	Odds ratio	95% CI
Average dose of drug (DDD) per day (quartiles) (referent not exposed)						
1st quartile	**1.57**	**1.40-1.76**	**2.98**	**2.60-3.41**	**2.20**	**1.83-2.63**
2nd quartile	**1.61**	**1.41-1.84**	**2.40**	**2.08-2.77**	**1.49**	**1.19-1.88**
3rd quartile	**1.57**	**1.37-1.81**	**1.97**	**1.58-2.45**	**1.34**	**1.03-1.74**
4th quartile	**1.45**	**1.24-1.69**	**1.98**	**1.65-2.38**	1.00	0.73-1.36
Age in 1-yr window	**1.03**	**1.02-1.03**	**1.03**	**1.02-1.03**	**1.03**	**1.02-1.04**
Male gender	**0.80**	**0.70-0.90**	**0.86**	**0.76-0.98**	**0.85**	**0.75-0.96**
Incident hyperlipidaemia	1.14	0.96-1.36	1.12	0.94-1.34	1.00	0.82-1.22
Incident CKD	**0.72**	**0.54-0.96**	0.77	0.58-1.03	0.75	0.56-1.00
Charlson Score	**1.17**	**1.12-1.23**	**1.16**	**1.10-1.22**	**1.18**	**1.12-1.24**
Blood pressure (Normal (≤150/90) referent)						
High (>150/90)	**1.24**	**1.15-1.35**	**1.30**	**1.20-1.41**	**1.29**	**1.19-1.40**
Not recorded	**0.89**	**0.82-0.96**	**0.83**	**0.77-0.91**	**0.80**	**0.74-0.87**
Body mass index (≤25 referent)						
>25	0.89	0.75-1.06	0.92	0.78-1.10	0.92	0.78-1.09
Not recorded	**0.72**	**0.62-0.83**	**0.76**	**0.65-0.88**	**0.76**	**0.66-0.88**
p for significance of test of goodness of fit*	0.08		0.09		0.08	

CI = confidence interval; DDD= defined daily dose; CKD = chronic kidney disease all stages (defined using Read codes found in appendix 2); Hyperlipidaemia defined using Read codes found in appendix 2

*Used Hosmer & Lemeshow test for model fit where non-significant test indicates model approximates the data i.e. good model fit

The results presented in table 7.5 show that gout patients who had been exposed to any of the three classes of medications used to treat vascular risk factors investigated were more likely to experience an incident vascular event than those that had not. The odds ratios were attenuated by increased exposure within all three classes of drugs, suggesting that those exposed to higher doses were less likely to have a first vascular event, and gout patients who were in the highest strata of exposure to lipid-lowering medications had no increased risk of experiencing a first vascular event. Other variables in the model influenced odds of vascular events in a similar way to that presented in section 7.4.3.

7.5 Limitations and strengths of this study

This section will discuss the limitations and strengths of this cohort study and the level of generalisability that results from these.

7.5.1 Limitations

Data Source

The use of data from routinely collected primary care EHR is accepted as a cost-effective way to undertake epidemiological studies of large patient populations across a broad population spread. (Jordan et al, 2006) The CPRD is the largest database of primary care EHR in the world, containing anonymised data for approximately 5.5% of the population of England and Wales. This data set was formally known as the General Practice Research Database (GPRD). Currently over 650 general practices contribute nationally representative data with over 5

million active patients. (www.cprd.com/intro.asp last accessed 14/06/2014) Practices must meet rigorous standards for data quality prior to inclusion and the high validity of diagnosis in the CPRD has been reported by two systematic reviews. (Herrett et al, 2010; Khan et al, 2010a)

Datasets such as the primary care EHR used for retrospective cohort studies are not collected for the express purpose of answering a particular research question, resulting in the inability to specify the particular variables of interest about which information is collected. Thus, levels of missing data for some of the variables of particular interest in this study, especially BMI, levels of serum urate, and exposure to smoking and alcohol, within the dataset were higher than would have been liked. In addition, it was felt that this data was not likely to be missing at random and as such the assumptions required for use of multiple imputation would not be satisfied. (Taylor et al, 2013) Some variables which may have a bearing on the relationships examined, such as family history of heart disease and physical activity, could not be included in the analysis due to poor levels of recording. Similarly, whilst matching by general practice is an accepted method of accounting for socio-demographic differences, there may be considerable socio-demographic variation within a practice area that may influence this relationship, and no individual level data was available, meaning that any potential effect could neither be accounted for in the analysis, nor explored any further.

Confounding by Indication

Confounding by indication, also known as confounding by severity of disease, results from the effect of prognostic factors on treatment decisions and produces a biased estimate of the treatment's effect on the outcome of interest. The most

obvious example of this is that those participants with the most severe disease are most likely to receive treatment, but are also more likely to experience complications or poorer outcomes. This can result in treatment's looking harmful, when in fact they are not, simply because those who receive them are more likely to experience the outcome of interest for reasons unrelated to the treatment itself.

Differences between participants in the likelihood of receiving treatments can be difficult to account for, and this must be highlighted as a major limitation to the examination of the effect of treatments on vascular risk in the gout-exposed group. Propensity scoring is one technique that could be used to address confounding by indication in future studies, using measures of relevant prognostic factors to model the likelihood of a participant receiving the treatment of interest. (Rosenbaum & Rubin, 1983) Since the accuracy of the propensity score is dependent upon the information used to specify it, large numbers of variables are often needed as predictors, not only confounders but also all other variables thought likely to influence likelihood of receiving treatment.

The propensity score can be entered into a regression model as a covariate, or can be used to match participants who do and do not receive the treatment but who have the same propensity score, (have similar prognostic factors and likelihood of receiving the treatment whether in fact they actually receive it). This allows the effect of treatments on the outcome of interest to be compared between those who do and do not receive treatment but are similar in other respects.

In this study, each participant has multiple exposure intervals, during which they either received a treatment or did not, and using a binary outcome variable to reflect this, propensity scores could be calculated using parameter estimates from

a mixed-effects logistic regression analyses, which include a random subject effect to account for the multiple observations within each subject. (Umbrello et al, 2012)

However there is evidence to suggest that propensity scoring does not perform well in the presence of missing data, since assumptions about the nature and ignorability of the missing data will need to be made. (Hill, 2004) As mentioned in section 7.5.1 missing data is a limitation of this study. A number of techniques for estimating propensity scores in the presence of missing data have been suggested including complete case analysis (Little & Rubin, 1987) and multiple imputation. (D'Agostino et al, 2000) Complete case analysis uses only participants with complete data, excluding those where there are missing data. This makes the assumption that those participants removed are a random sample of the whole dataset with respect to the covariates, and also reduces the size of the study sample. (Hill, 2004) The most frequently applied approach is that of multiple imputation, whereby missing values are replaced by "draws" from a predictive distribution, allowing analysis of a complete dataset. (Rubin, 1987) However, multiple imputation also requires that the assumption that the data is missing at random be satisfied, which as described in section 7.5.1 was not felt to be the case in this study.

Nevalainen et al, 2009, proposed a two-fold fully conditional specification algorithm to impute missing data in longitudinal data. It imputes missing values at a given time point, conditional on information at the same time point and immediately adjacent time points. The application of this procedure to similar data has been outlined in Welch et al, 2014, however since the estimation of treatment effects in the gout-exposed patients formed only a small part of this thesis it was not applied

here due to the constraints of time. Future investigations could incorporate this approach to impute missing data allowing the estimation of propensity scores to account for differences between subjects who received treatments, and those who did not, and minimise the effect of confounding by indication.

Study design

A further limitation of this work is the nature of the study itself. To take into account differences between exposed and unexposed groups, multiple adjustments on risk factors for vascular events have been performed. However, even if the main risk factors have been taken into account, residual confounding effects cannot be ruled out. Moreover, as an epidemiological study design, although an association can be demonstrated, causation cannot be inferred.

Gout participant identification

This study used diagnostic codes Read codes attached to episodes of care recorded within the electronic primary care medical record as the definition of gout. Recording of these codes is based upon primary care diagnosis, usually made on clinical grounds, without aspiration and examination of synovial fluid for the presence of MSU crystals. This introduces the potential for misclassification bias, although previous studies indicate reasonable validity of gout diagnosis in primary care, (Roddy et al, 2007; Roddy et al, 2010) and previous studies undertaken in the CPRD have selected gout cases using a primary care diagnosis. (Mikuls et al, 2005a; Mikuls et al, 2005b)

Coding of events

It follows therefore, that the use of Read codes to identify outcomes of interest, may also risk misclassification bias. Particularly in cardiovascular disease, terminology used to describe events has changed over time, and thus coding behaviours of GPs may also have changed over time. Whilst every effort has been made to use the most specific codes, terms such as Acute Coronary Syndrome could describe either MI or unstable angina, and common use of more generalised codes for cerebrovascular disease potentially adds to the risk of misclassification. However, validity of coding has been shown to be high in the CPRD (Khan et al, 2010; Herrett et al, 2010)

7.5.2 Study Strengths

This study has a number of strengths compared with existing literature. This is the largest study to examine the association of gout with incident vascular disease in primary care patients to date. Furthermore, it is the first study to examine risk of incident peripheral vascular disease in primary care gout patients.

The use of a large number of well-validated primary care EHR means the study is generalisable to the wider population of gout patients. Validity of cardiovascular disease diagnoses in CPRD was assessed by a recent systematic review, which reported a positive predictive value of diagnosis of myocardial infarction coded in CPRD of over 80%, and comparable reliability of coding for ischaemic heart disease to other primary care databases. (Khan et al, 2010a) The exclusion of patients with a prior history of vascular events reduced both surveillance bias and

the additional risk conferred by a vascular history, allowing the contribution of gout itself to be more accurately investigated.

In addition, matching patients by age, gender and GP practice reduces the risk of socio-demographic confounding, whilst the adjustment for potential explanatory covariates in two models, allows more accurate examination of contribution of particular risk factors, and removes the element of surveillance bias associated with disease monitoring for other chronic conditions such as hypertension and diabetes.

7.6 Summary

This section has described and reported the sub-group analysis of the retrospective cohort study investigating the effect of risk factors in gout patients who experience vascular events and those who do not, using techniques of logistic regression and multilevel discrete-time event history analysis. This investigation found that poor surveillance of SUA was associated with increased risk of experiencing a first vascular event, whilst frequent consultation for gout reduced this risk, highlighting the role of surveillance in reduction of vascular risk in gout patients.

Gout patients who were exposed to prescribed NSAIDs and uricosurics, as well as drugs used to treat vascular risk factors were more likely to experience a first vascular event, a difference in the result of exposure to these medications to that which might be expected, suggesting mechanisms that underlie this additional risk in patients with gout are different to those in the general population. Exposure to allopurinol did not influence the risk of experiencing a vascular event. However,

the effect of cumulative exposure to these medications (including prior to diagnosis of gout), and the time since most recent prescription for these medicines, on the risk of experiencing a first vascular event remains unclear. This will be investigated in subsequent chapters.

Chapter 8: Nested case-control study examining the association between drug exposures and risk of vascular event in the gout group

8.1 Overview

Chapter 7 identified an increased risk of incident vascular event in gout patients exposed to medications used in the treatment of gout and the treatment of vascular risk factors, following their diagnosis of gout. This chapter will describe the use of a nested case-control study to further investigate the effect of both cumulative exposure (including prior to the diagnosis of gout), and time since most recent prescription of these medications on the risk of an incident vascular event in patients with gout to test the hypothesis that the effect of exposure to these groups of medications on the risk of vascular event differs according to cumulative exposure and time since most recent exposure. Choice of study design, the methodology of selecting cases and controls and identifying exposures and the statistical analyses chosen will be presented, followed the results and potential implications of these findings.

8.2 Background

This section will describe the rationale for undertaking the study and choice of study design.

8.2.1 Rationale

Whilst it is clear from the retrospective cohort study that gout is an independent risk factor for vascular disease, it remains unclear why some gout patients suffer vascular events, whilst others do not. Exposures to certain medications such as aspirin and statins may confer protection against vascular disease, (Antithrombotic Trialists' Collaboration, 1994; Antithrombotic Trialists' Collaboration, 2002; Naci et al, 2013) whereas exposure to others, such as non-steroidal anti-inflammatory drugs, may increase risk of vascular events. (Bhala et al, 2013) The results of the multilevel discrete-time event history analysis presented in chapter 7 suggest that contemporaneous exposure to medications used to treat both acute and chronic gout, and those used to treat vascular risk factors (e.g. hypertension and hyperlipidaemia) or the mechanisms underlying vascular risk (e.g. anti-platelet medications) following diagnosis of gout does not seem to reduce the risk of an incident vascular event as might be expected. The reasons for this are unclear, as is the influence of cumulative exposure to these medications (including prior to diagnosis of gout) on the risk of a vascular event, and time since most recent prescription for the drug.

The clarification of these relationships will inform clinical decision making, since if patients currently taking the medications of interest (particularly urate-lowering therapy and medications used to treat vascular risk factors) are less likely to experience a vascular event than those who have previously taken, but discontinued them, this would provide justification for indefinite prescribing and encourage patient compliance. However, if there are other medications of interest (particularly NSAIDs) whereby cumulative exposure might increase the risk of an

incident vascular event, then this might justify recommendations to prefer colchicine over NSAIDs in the treatment of, and prophylaxis against, acute flares of gout whilst initiating urate-lowering therapy in those at high vascular risk, or in those who have previously had high cumulative exposure to NSAIDs.
Therefore a nested case-control study was used to examine these relationships, which will then be compared with the results presented in chapter 7 to identify differences between cumulative exposures and those which follow diagnosis of gout.

8.2.2 Choice of study design

As discussed in chapter 4, the case-control design identifies patients with a particular outcome of interest, matches them to controls who have not experienced that outcome of interest, and looks retrospectively at particular exposures to determine whether these exposures influence the risk of experiencing the outcome of interest. This is in contrast to the cohort study where patients are selected based upon their exposure to a particular disease and followed until they do or do not develop an outcome of interest. The retrospective cohort study presented in chapters 5, 6 and 7 compared risk of vascular events in those with gout to those without gout and identified gout as an independent risk factor for vascular disease, and the subgroup analyses presented in chapter 7 investigate which factors following the diagnosis of gout may predispose some gout patients to experience vascular events whilst others do not. These findings suggest that the mechanism underlying excess vascular risk in patients with gout differs from that in the general population, and that exposure to medications that should make experiencing a

vascular event less likely including urate lowering therapy, anti-inflammatories and medications to treat vascular risk factors, following diagnosis of gout, do not attenuate this risk as expected.

The case-control design was chosen in order to allow comparison of cumulative exposure to medications of interest (including prior to diagnosis of gout), and most recent prescription for these drugs in patients with gout who experienced a first vascular event of interest, with those who did not. Use of a nested case-control design allowed comparison of groups of gout patients based on outcome of interest (vascular event), whilst matching by age, gender and general practice to reduce potential confounding. It allows a more accurate comparison of the predictors of vascular event in those who experience a vascular event compared with those who do not, rather than the contribution of each covariate to overall vascular risk across all participants. It also facilitates investigation of a number of exposures simultaneously.

8.3 Matching of cases and controls

This section describes the identification and matching of cases and controls for the nested case-control analysis from within the cohort.

8.3.1 Eligibility for inclusion

Since the study design is a nested case-control study, where the case and control population are selected from the existing cohort study population, all gout patients from the retrospective cohort study described above were eligible for inclusion.

8.3.2 Case definition

Cases were defined as those gout patients from the cohort who had experienced any type of vascular event during the follow-up period. The codes used to identify vascular events of interest are shown in Appendix 2

8.3.3 Control selection

Controls were defined as those gout patients from the cohort who had not experienced any type of vascular event during the follow-up period. Patients who had experienced a vascular event (cases) were eligible to act as controls in the period of their follow-up prior to their event, providing that the time of interest was after their diagnosis of gout and that this part of their follow-up was included in the original study data. (Lubin & Gail, 1984; Robins et al, 1986)

8.3.4 Matching of cases and controls

All gout patients who had experienced a vascular event during the original cohort study follow-up were matched to at least one control gout patient who had not experienced a vascular event. They were matched using the same matching variables described in section 4.4.2 (year of birth, gender and registered general practice) to minimise confounding (as described in section 4.4.2). In addition controls were also required to be alive at the time their matched case experienced the vascular event, having survived event free until that point.

8.4 Exposures of interest

Exposures of interest included any drugs which may influence the likelihood of vascular events. Those chosen included drugs used in the treatment of acute and chronic gout (colchicine, NSAIDs, allopurinol and uricosurics) and drugs used to treat vascular risk factors or mechanisms underlying vascular risk in the anti-platelet, lipid-lowering and anti-hypertensive groups (shown in Table 8.1). The reasons for their inclusion were similar to those presented in section 7.3.

Table 8.1 Medications of interest

Anti-platelet	Lipid-lowering	Anti-hypertensives
Aspirin	HMG CoA reductase inhibitors ("statins")	ACE inhibitors (e.g. ramipril)
Clopidogrel	Fibrates (e.g. fenofibrate)	A II receptor antagonists (e.g. candesartan)
Dipyridamole	Selective cholesterol uptake inhibitors (e.g. ezetimibe)	α-adrenergic receptor antagonists (e.g. doxazosin) but excluding those only used for benign prostatic hypertrophy (e.g. tamsulosin) β-adrenergic receptor antagonists (e.g. atenolol) Calcium channel receptor antagonists (e.g. amlodipine) Centrally acting anti-hypertensives (e.g. methyldopa) Diuretics (e.g. bendroflumethiazide) Vasodilator anti-hypertensives (e.g. hydralazine)
HMG CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; ACE = angiotensin-converting enzyme; A II = angiotensin II		

Exposures were identified within the electronic health record (EHR) using codes returned by the CPRD browser. These were then used to examine the effect of cumulative exposure to each group of drugs and the temporal relationship of these exposures to vascular event.

8.4.1 Cumulative exposure to medication

Cumulative exposure to medications of interest was investigated in order to more accurately establish predictors of vascular risk in patients with gout by comparing exposures in those who had a vascular event with those who did not. Given that in the results presented in sections 7.4.3 and 7.4.4, exposures following diagnosis of gout did not all influence the risk of experiencing a vascular event in a way that would be expected, and that the exposures investigated were measured per year following diagnosis of gout, rather than cumulatively, it seems reasonable to extend the investigation of exposures to include cumulative exposure since duration of therapy may be an important factor in their influence on vascular risk. This lends clinical utility to the estimate of risk associated with the exposure, since demonstrating that duration of therapy is important may justify earlier initiation of these drugs, or even multi-drug primary prevention strategies in patients with gout, whereas demonstration of lack of influence on vascular risk in patients with gout may prompt investigation of other strategies by which to manage vascular risk in gout.

Cumulative exposure to medications was assessed by calculating prescribed dosage and duration of exposure which was then converted to the defined daily

dosage (as described in section 7.3.4) and summed to give a cumulative exposure until a vascular event was experienced or until dummy date equivalent to the date of vascular event experienced by the case to which they were matched for controls. Exposure to each group of drugs was then categorised into above and below median exposure (with no exposure as the referent category) as the cumulative levels of exposure varied significantly and so to include this as a continuous variable would have yielded an odds ratio per unit increase in DDD that was too small to be of practical value.

8.4.2 Time since most recent prescription for medications of interest and odds of vascular event

The previous investigation presented in sections 7.4.3 and 7.4.4 allowed exposure to medications of interest to vary year by year, however any difference in risk of vascular event between those currently using, having recently used or having used the drugs in the past could not be assessed. The clinical rationale for investigating the risk of experiencing a vascular event according to most recent use of the drug is to start to understand patterns in how drugs influence vascular risk, for example, if exposure to a particular medication within two years but not five years reduced odds of a vascular event then this provides evidence that benefit of these drugs is lost if they are stopped, providing justification for indefinite prescribing, and encouraging improved patient compliance.

Temporal relationship of the prescription of particular drugs with vascular event was ascertained by categorising into four mutually exclusive time windows: most

recent exposure within two years of date of vascular event/matched date for controls, between two and five years and more than five years from date of vascular event or matched date for controls, and those who had never been exposed (no recorded use at any time prior to date of vascular event) which became the referent category.

Due to the small numbers of participants in each group, when investigating combinations of drugs, exposure was classified into ever exposed compared with never exposed (prior to the date of vascular event).

8.5 Explanatory covariates

As discussed in section 2.4.2, many factors contribute to an individual's likelihood of developing vascular disease. In considering the role played by exposures of interest in the likelihood of subsequent vascular disease following a diagnosis of gout, these other factors which may influence this relationship must be accounted for. Those considered important in this study will be discussed here.

8.5.1 Adjustment for explanatory covariates

In order to account for the role that other factors play in the risk of developing vascular disease after a diagnosis of gout, similar potential confounders to those described in section 5.4 were introduced into the analysis. These were:

- age at diagnosis of gout
- dichotomised values for being over-weight (BMI ≥ 25kg/m^2 yes/no/missing)
- ever/never/missing exposure to smoking or alcohol
- Charlson Co-morbidity Index score
- hypertension
- renal disease (defined as chronic kidney disease or acute/chronic renal failure)
- hyperlipidaemia

8.6 Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the sample including patient demographics and presence of co-morbidities. Odds ratio and 95% confidence intervals of vascular event associated with current, recent and past exposure to each group of drugs as well as cumulative exposure above and below the median exposure to that group of drugs were calculated using conditional logistic regression. All analysis was conducted using Stata statistical software release 12 (StataCorp: College Station, TX, 2011).

8.7 Results

8.7.1 Number of cases and controls

In the original cohort study, 2409 gout patients experienced a vascular event. Of these, 437 had at least one exact matched control for year of birth, gender and registered general practice who did not experience a vascular event during the follow-up period in question. Thus, the final patient population included 437 cases (gout patients who had experienced a vascular event) and 437 controls (gout patients who had not experienced a vascular event); a total of 874 patients.

8.7.2 Description of the study population

The majority of patients included were male (79.9% n=698), and as cases and controls were matched on gender so the proportion of males and females in each group was similar. Year of birth was also a matching variable and so mean age at diagnosis of gout in the study population overall was 65.1 years (SD 9.1), and mean age at event/dummy date was 70.3 years (SD 8.9). Both were similar in those who experienced a vascular event and their matched controls. Mean duration of exposure to gout was also similar, 5.3 years (SD 3.4) at event/dummy date for cases and 4.9 years (SD 2.8) for controls. Table 8.2 shows the frequency and percentage of vascular risk factors in cases and controls.

Table 8.2 Frequency and percentage of vascular risk factors in cases and controls

Vascular risk factor	Cases	Controls	p for significance of difference *
	N (%)	N (%)	
Pre index hypertension	187 (42.8%)	152 (34.8%)	<0.01
Pre index hyperlipidaemia	33 (7.6%)	23 (5.3%)	0.04
Pre index diabetes	14(3.2%)	9 (2.1%)	0.17
Pre index renal disease	7 (1.6%)	4 (0.9%)	0.41
BMI >25 kg/m^2	291 (66.6%)	269 (61.6%)	0.10
History of alcohol consumption	354 (81.0%)	364 (83.3%)	0.07
Current/former smoker	137 (31.4%)	115 (26.3%)	<0.01
BMI=body mass index; * statistical significance assessed using Chi-squared test			

From table 8.2, it can be seen that the prevalence of hypertension, hyperlipidaemia, diabetes, renal disease, being overweight and smoking was slightly higher at diagnosis of gout in those who went on to experience a vascular event than those who did not, although this difference was only statistically significant for hypertension, hyperlipidaemia and smoking exposure. History of alcohol consumption was more prevalent in those who did not experience a vascular event, although this difference was not statistically significant.

Of the 437 gout patients who experienced a vascular event, the frequency and percentage of types of incident vascular event experienced are shown in table 8.3. The majority n=250 (57.2%) experienced cardiovascular events.

Table 8.3: Frequency and percentage of types of incident vascular event experienced

	N	% of all first vascular events
All vascular events	437	100
All cardiovascular events (not including those coded as angina or MI)	250 (130)	57.2 (29.7)
Angina	71	16.2
MI	49	4.3
All cerebrovascular events (not including those coded as TIA or CVA)	160 (74)	36.6 (16.9)
CVA	45	10.3
TIA	41	9.4
PVD	27	6.2
MI = myocardial infarction; CVA = cerebrovascular accident; TIA= transient ischaemic attack; PVD = peripheral vascular disease		

8.7.3 Frequency and percentage of prescriptions for drugs of interest in cases and controls

Tables 8.4a and 8.4b demonstrate the distribution of prescriptions for the drugs of interest in relation to the event or dummy date for cases and controls. Those used to treat gout are shown in table 8.4a, and drugs used to treat vascular risk factors are shown in 8.4b. The drugs included to treat vascular risk factors are described in section 7.3.3.

The number of patients prescribed uricosuric medications was too small to allow further meaningful analysis, and so no further results are presented relating to this class of drugs.

Table 8.4a: Distribution of prescriptions for drugs used to treat gout

Date of most recent prescription in relation to vascular event/dummy date	Allopurinol N (%)		Uricosurics N (%)		Colchicine N (%)		NSAIDs N (%)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
0-2 years	123 (28.1)	112 (25.6)	3 (0.7)	1 (0.2)	30 (6.9)	17 (3.9)	282 (64.5)	269 (61.6)
2-5 years	13 (3.0)	19 (4.3)	2 (0.5)	0	12 (2.7)	15 (3.4)	86 (19.7)	94 (21.5)
More than 5 years	11 (2.5)	11 (2.5)	2 (0.5)	0	17 (3.9)	5 (1.1)	45 (10.3)	51 (11.7)
Never	290 (66.4)	295 (67.5)	430 (98.3)	436 (99.8)	353 (86.5)	400 (91.5)	24 (5.5)	23 (5.3)
Total	437	437	437	437	437	437	437	437
NSAIDs = Non-steroidal anti-inflammatory drugs								

Table 8.4b: Distribution of prescriptions for drugs used to treat vascular risk factors

Date of most recent prescription in relation to vascular event/dummy date	Antiplatelet N (%)		Lipid-lowering N (%)		Antihypertensives N (%)	
	Cases	Controls	Cases	Controls	Cases	Controls
0-2 years	244 (55.8)	57 (13.0)	130 (29.7)	32 (7.3)	361 (82.6)	234 (53.5)
2-5 years	6 (1.4)	4 (0.9)	4 (0.9)	1 (0.2)	11 (2.5)	23 (3.0)
More than 5 years	2 (0.5)	9 (2.1)	1 (0.2)	1 (0.2)	3 (0.7)	20 (2.3)
Never	180 (42.3)	367 (84.0)	302 (69.1)	402 (92.2)	62 (14.2)	180 (41.2)
Total	437	437	437	437	437	437

8.7.4 Results of conditional logistic regression

This section will describe the results of the conditional logistic regression, examining the relationship between prescription of drugs of interest and likelihood of incident vascular disease in patients with gout.

8.7.4.1 Univariate analysis

The odds ratio of experiencing a vascular event in patients with gout when having been exposed to the drug of interest within 2 years, 2-5 years and more than 5 years previously, compared to never having been exposed to the drug is shown below. Table 8.5a shows the odds ratios and 95% confidence intervals for prescription of drugs used to treat gout, and table 8.5b shows the odds ratios and 95% confidence intervals for prescription of drugs used to treat vascular risk factors.

Table 8.5a: Risk of vascular event associated with drugs used to treat gout

Most recent prescription in relation to event/dummy date	Odds Ratio (95% CI)		
	Allopurinol	Colchicine	NSAIDs
Reference value: Never exposed			
0-2 years	1.12 (0.90-1.40)	**1.85 (1.19-2.89)**	1.01 (0.65-1.55)
2-5 years	0.71 (0.43-1.18)	0.83 (0.46-1.52)	0.87 (0.55-1.38)
More than 5 years ago	1.02 (0.56-1.84)	**3.37 (1.67-6.83)**	0.83 (0.49-1.40)
CI = confidence interval; NSAIDs = non-steroidal anti-inflammatory drugs			

Table 8.5a shows that exposure to allopurinol or NSAIDs does not influence the risk of experiencing a vascular event. In contrast, exposure to colchicine within two years and more than 5 years from vascular event made a vascular event more likely, with greater odds in those who were most recently prescribed colchicine more than 5 years before the vascular event.

Table 8.5b: Risk of vascular event associated with drugs used to treat vascular risk factors

Most recent prescription in relation to event/dummy date	Odds Ratio (95% CI)		
	Antiplatelet	Lipid-lowering	Anti-hypertensives
Referent value: never exposed			
0-2 years	**9.51 (6.98-12.94)**	**7.67 (5.26-11.17)**	**4.27 (3.32-5.48)**
2-5 years	2.34 (0.76-7.18)	**7.98 (1.14-55.65)**	**2.24 (1.13-4.46)**
More than 5 years	0.22 (0.04-1.29)	2.77 (0.72-10.66)	1.11 (0.40-3.09)
CI = confidence interval			

Table 8.5b shows that exposure to anti-hypertensives, anti-platelet and lipid-lowering medications within 2 years made a vascular event more likely. Additionally, exposure to lipid-lowering and anti-hypertensive medications within 2-5 years also made vascular event more likely, although whilst the risk of experiencing an event increased with time since most recent prescription for lipid-lowering medications, it did reduce but remain increased with time since exposure to anti-hypertensive medications.

The odds of vascular event according to cumulative exposure to each group of drugs above and below the median are shown below. Table 8.6a shows the odds ratio and 95% confidence intervals associated with exposure to drugs used to treat

gout, and table 8.6b shows the odds ratio and 95% confidence intervals associated with exposure to drugs used to treat vascular risk factors.

Table 8.6a: Cumulative exposure to drugs used to treat gout and relationship to odds of vascular event

Cumulative exposure	Allopurinol Odds Ratio (95%CI)	Colchicine Odds Ratio (95%CI)	NSAIDs Odds Ratio (95%CI)
Referent value: Never exposed			
Below median	1.16 (0.83-1.64)	1.38 (0.77-2.48)	0.71 (0.46-1.11)
Above median	0.90 (0.62-1.31)	1.66 (0.88-3.12)	**0.50 (0.31-0.80)**
CI = Confidence interval; NSAIDs = Non-steroidal anti-inflammatory drugs			

Table 8.6a shows that the risk of a vascular event is unaffected by level of cumulative exposure to allopurinol and colchicine. Above median exposure to NSAIDs is shown to reduce risk of a vascular event.

Table 8.6b: Cumulative exposure to drugs used to treat vascular risk factors and relationship to odds of vascular event

Cumulative exposure	Antiplatelet Odds Ratio (95%CI)	Lipid-lowering Odds Ratio (95%CI)	Antihypertensives Odds Ratio (95%CI)
Referent value: Never exposed			
Below median	**2.12 (1.57-2.88)**	**3.63 (2.63-5.01)**	**1.97 (1.30-2.98)**
Above median	**2.85 (1.97-4.13)**	**4.02 (2.73-5.93)**	**1.65 (1.03-2.64)**
CI = Confidence interval			

Table 8.6b shows that participants exposed to anti-platelet, lipid-lowering and anti-hypertensive medications are more likely to experience a vascular event, with those who had above median exposure to anti-platelet and lipid-lowering medications more likely to experience a vascular event than those with below median exposure. In contrast, those with above median exposure to anti-hypertensives were less likely to experience a vascular event than those with below median exposure, but still more likely than those who were unexposed.

8.7.4.2 Multivariable analysis

The odds ratio of experiencing a vascular event in patients with gout who are prescribed drugs of interest compared to those who are not, after adjustment for age at diagnosis of gout, gender, history of hypertension, hyperlipidaemia, renal disease, Charlson co-morbidity score, overweight (BMI>25kg/m^2 yes/no), ever/never exposure to smoking or alcohol, are presented in tables 8.7a and 8.7b below. Table 8.7a presents the odds ratio and 95% confidence intervals associated with exposure to drugs used to treat gout, and table 8.7b presents the odds ratio and 95% confidence intervals associated with exposure to drugs used to treat vascular risk factors.

Table 8.7a: Multivariable analysis – drugs used to treat gout

	Odds Ratio (95% CI)		
	Allopurinol	Colchicine	NSAIDs
Most recent prescription in relation to event/dummy date (referent: never exposed)			
0-2 years	0.99 (0.68-1.45)	1.25 (0.73-2.14)	1.69 (0.90-3.16)
2-5 years	0.57 (0.31-1.03)	0.61 (0.33-1.13)	1.20 (0.64-2.26)
More than 5 years	0.64 (0.32-1.28)	**3.12 (1.47-6.65)**	1.03 (0.54-1.95)
Cumulative exposure DDD: Referent value: never exposed			
Below median	1.28 (0.90-1.82)	1.72 (0.94-3.14)	0.67 (0.42-1.06)
Above median	0.95 (0.63-1.43)	**2.00 (1.09-3.70)**	**0.44 (0.27-0.74)**
Age at diagnosis of gout	**0.93 (0.88-0.99)**	**0.92 (0.87-0.98)**	**0.91 (0.86-0.97)**
Overweight (BMI >25kg/m^2): Referent value: no			
Yes	1.17 (0.91-1.49)	1.17 (0.91-1.50)	1.15 (0.89-1.47)
Missing	0.76 (0.50-1.15)	0.85 (0.55-1.30)	0.73 (0.48-1.11)
Ever exposure to alcohol: Referent value: no exposure			
Yes	**0.67 (0.48-0.93)**	**0.69 (0.50-0.96)**	**0.70 (0.51-0.98)**
Missing	0.77 (0.47-1.28)	0.78 (0.46-1.31)	0.83 (0.50-1.36)
Ever exposed to smoking: Referent value: no exposure			
Yes	1.20 (0.95-1.52)	1.18 (0.94-1.49)	1.23 (0.97-1.56)
Missing	0.79 (0.60-1.07)	0.76 (0.56-1.02)	0.80 (0.60-1.08)
Charlson co-morbidity score	**1.25 (1.09-1.43)**	**1.28 (1.14-1.45)**	**1.26 (1.10-1.45)**
Hypertension	**1.40 (1.13-1.74)**	**1.42 (1.14-1.76)**	**1.40 (1.13-1.73)**
Hyperlipidaemia	1.38 (0.91-2.08)	**1.56 (1.03-2.37)**	1.35 (0.90-2.01)
Renal disease	1.03 (0.38-2.77)	1.02 (0.36-2.87)	0.98 (0.35-2.74)
CI = confidence interval; DDD = defined daily dosage; NSAIDs = non-steroidal anti-inflammatory drugs			

Table 8.7a shows that in the multivariable model, exposure to allopurinol does not influence the risk of experiencing a vascular event, most recent exposure more than 5 years previously and above median exposure to colchicine made a vascular event more likely whilst above median exposure to NSAIDs reduced the odds of a vascular event. Presence of hypertension and increasing Charlson co-morbidity score increased odds of a vascular event, whereas increasing age at diagnosis of gout and exposure to alcohol made a vascular event less likely.

Table 8.7b: Multivariable analysis – drugs used to treat vascular risk factors

	Odds Ratio (95% CI)		
	Antiplatelet	Lipid-lowering	Antihypertensives
Most recent prescription in relation to event/dummy date (referent: never exposed)			
0-2 years	**4.86 (3.20-7.37)**	**2.91 (1.85-4.59)**	**3.37 (2.36-4.81)**
2-5 years	1.62 (0.55-4.79)	3.09 (0.30-31.56)	1.50 (0.74-3.03)
More than 5 years	0.18 (0.03-1.15)	0.45 (0.13-1.63)	0.96 (0.33-2.81)
Cumulative exposure DDD: Referent value: never exposed			
Below median	**2.20 (1.59-3.03)**	**3.63 (2.55-5.18)**	**1.94 (1.27-2.95)**
Above median	**3.14 (2.12-4.66)**	**4.55 (2.96-7.00)**	**1.63 (1.01-2.65)**
Age at diagnosis of gout	**1.48 (1.17-1.87)**	**0.90 (0.84-0.96)**	**0.93 (0.88-0.98)**
Overweight (BMI >25kg/m^2):Referent value: no			
Yes	1.14 (0.83-1.56)	1.04 (0.78-1.38)	0.95 (0.72-1.24)
Missing	0.72 (0.42-1.23)	1.08 (0.68-1.73)	**0.57 (0.37-0.88)**
Ever exposure to alcohol: Referent value: no exposure			
Yes	0.76 (0.48-1.21)	0.68 (0.46-1.00)	**0.59 (0.41-0.84)**
Missing	0.85 (0.39-1.86)	0.92 (0.54-1.58)	0.80 (0.45-1.40)
Ever exposed to smoking: Referent value: no exposure			
Yes	1.28 (0.96-1.71)	1.23 (0.94-1.61)	1.15 (0.90-1.48)
Missing	0.94 (0.64-1.37)	0.75 (0.54-1.05)	0.80 (0.45-1.40)
Charlson co-morbidity score	**1.48 (1.17-1.87)**	**1.32 (1.16-1.51)**	**1.26 (1.11-1.44)**
Hypertension	1.15 (0.89-1.49)	1.25 (1.00-1.57)	N/A
Hyperlipidaemia	**1.81 (1.03-3.19)**	N/A	1.27 (0.81-1.97)
Renal disease	1.33 (0.26-6.88)	0.59 (0.20-1.74)	0.60 (0.23-1.61)
CI = confidence interval; DDD = defined daily dosage; NSAIDs = non-steroidal anti-inflammatory drugs			

Table 8.7b shows patients exposed to anti-platelet, anti-hypertensive and lipid-lowering medications within two years are more likely to experience a vascular event in the multivariable model. Odds of experiencing a vascular event was increased with both above and below median exposures to all three classes of drugs, with risk greater in those with above median exposure to anti-platelet and lipid-lowering medications. In contrast, those with above median exposure to anti-hypertensives were less likely to experience a vascular event than those with below median exposure, but still more likely than those who were unexposed.

Table 8.8a reports the odds ratio of experiencing a vascular event given exposure to combinations of medications without adjustment for other vascular risk factors, table 8.8b reports the odds ratio of experiencing a vascular event given exposure to combinations of medications used to treat vascular events in the full multivariable model. Table 8.8c reports the odds ratio of experiencing a vascular event given exposure to combinations of medications used to treat vascular events and allopurinol in the multivariable model.

These tables show that even in combination, exposure to the medications used to treat vascular risk factors does not reduce the risk of experiencing an incident vascular event. However, those participants exposed to allopurinol were less likely to experience an incident vascular event if that exposure was also in the presence of combinations of:

- anti-hypertensives and anti-platelet drugs
- anti-platelet and lipid-lowering drugs
- anti-hypertensive, anti-platelet and lipid-lowering

Table 8.8a Odds ratio of experiencing a vascular event following exposure to combinations of medications

Combination of medications (ever compared with never exposure)	Anti-hypertensive + anti-platelet	Anti-hypertensive + lipid-lowering	Anti-platelet + lipid-lowering	Anti-hypertensive + anti-platelet + lipid-lowering	Anti-hypertensive + anti-platelet + lipid-lowering + allopurinol
	OR(95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anti-hypertensives	**1.74 (1.41-2.14)**	**1.97 (1.61-2.42)**		**1.72 (1.39-2.12)**	**1.77 (1.43-2.18)**
Anti-platelet	**3.50 (2.52-4.86)**		**3.09 (2.24-4.26)**	**2.82 (2.05-3.88)**	**3.02 (2.18-4.20)**
Lipid-lowering		**5.66 (3.76-8.52)**	**4.30 (2.82-6.57)**	**4.21 (2.76-6.41)**	**4.34 (2.87-6.57)**
Allopurinol					**0.75 (0.63-0.88)**
Hosmer & Lemeshow p for goodness of fit	0.20	0.17	0.23	0.26	0.27
CI = confidence interval; OR = odds ratio					

Table 8.8b Odds ratio of experiencing a vascular event following exposure to combinations of medications used to treat vascular risk factors in a multivariable model

Combination of medications (Ever compared to never exposure)	Anti-hypertensive + anti-platelet	Anti-hypertensive + lipid-lowering	Anti-platelet + lipid-lowering	Anti-hypertensive + anti-platelet + lipid-lowering
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anti-hypertensives	**1.70 (1.37-2.10)**	**1.95 (1.58-2.40)**		**1.70 (1.36-2.11)**
Anti-platelet	**3.58 (2.55-5.01)**		**3.10 (2.22-4.32)**	**2.87 (2.06-3.99)**
Lipid-lowering		**5.79 (3.81-8.81)**	**4.33 (2.75-6.82)**	**4.34 (2.78-6.79)**
Overweight (BMI >25kg/m^2):Referent value: no				
Yes	1.11 (0.86-1.43)	1.10 (0.84-1.45)	1.09 (0.83-1.43)	1.08 (0.82-1.41)
Missing	**0.56 (0.36-0.87)**	0.73 (0.48-1.13)	0.67 (0.42-1.06)	**0.62 (0.39-0.97)**
Ever exposure to alcohol: Referent value: no exposure				
Yes	0.73 (0.50-1.07)	**0.65 (0.46-0.92)**	0.73 (0.50-1.07)	**0.67 (0.46-0.99)**
Missing	0.71 (0.38-1.31)	0.73 (0.42-1.24)	0.72 (0.40-1.31)	0.69 (0.39-1.24)
Ever exposure to smoking: Referent value: no exposure				
Yes	1.25 (0.95-1.63)	1.11 (0.86-1.44)	1.24 (0.93-1.65)	1.21 (0.90-1.62)
Missing	0.98 (0.73-1.33)	0.98 (0.72-1.33)	1.02 (0.74-1.41)	0.97 (0.70-1.36)
Charlson	**1.20 (1.04-1.38)**	**1.25 (1.10-1.42)**	**1.30 (1.14-1.49)**	**1.29 (1.12-1.47)**
Hypertension			1.21 (0.95-1.52)	
Hyperlipidaemia	1.15 (0.67-1.96)			
Renal disease	1.19 (0.32-4.46)	0.60 (0.22-1.60)	0.76 (0.26-2.28)	0.65 (0.20-2.09)
Hosmer & Lemeshow p for goodness of fit	0.22	0.19	0.26	0.28

CI = confidence interval; OR = odds ratio

Table 8.8c Odds ratio of experiencing a vascular event following exposure to combinations of medications used to treat vascular risk factors and allopurinol in a multivariable model

Combination of medications (Ever compared with never exposure)	Anti-hypertensive + anti-platelet + allopurinol	Anti-hypertensive + lipid-lowering + allopurinol	Anti-platelet + lipid-lowering + allopurinol	Anti-hypertensive + anti-platelet + lipid-lowering + allopurinol
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anti-hypertensives	**1.73 (1.40-2.15)**	**1.98 (1.61-2.44)**		**1.69 (1.36-2.10)**
Anti-platelet	**3.77 (2.67-5.30)**		**3.29 (2.36-4.61)**	**3.11 (2.24-4.31)**
Lipid-lowering		**5.88 (3.87-8.94)**	**4.42 (2.82-6.92)**	**4.33 (2.83-6.60)**
Allopurinol	**0.78 (0.66-0.91)**	0.87 (0.74-1.02)	**0.76 (0.64-0.90)**	**0.73 (0.63-0.89)**
Overweight (BMI >25kg/m^2):Referent value: no				
Yes	1.13 (0.87-1.46)	1.12 (0.86-1.47)	1.13 (0.86-1.49)	1.12 (0.85-1.47)
Missing	**0.54 (0.34-0.86)**	0.73 (0.47-1.13)	0.67 (0.41-1.08)	**0.61 (0.37-0.99)**
Ever exposure to alcohol: Referent value: no exposure				
Yes	0.75 (0.51-1.10)	**0.65 (0.46-0.93)**	0.76 (0.51-1.13)	0.72 (0.49-1.07)
Missing	0.74 (0.39-1.39)	0.74 (0.43-1.27)	0.75 (0.40-1.39)	0.71 (0.38-1.31)
Ever exposure to smoking: Referent value: no exposure				
Yes	1.26 (0.96-1.66)	1.12 (0.87-1.44)	1.27 (0.95-1.70)	1.22 (0.91-1.64)
Missing	0.99 (0.73-1.33)	0.98 (0.72-1.33)	1.04 (0.75-1.43)	1.04 (0.76-1.44)
Charlson	**1.19 (1.03-1.37)**	**1.25 (1.10-1.41)**	**1.29 (1.13-1.48)**	**1.25 (1.10-1.43)**
Hypertension			1.21 (0.95-1.52)	
Hyperlipidaemia	1.18 (0.68-2.04)			
Renal disease	1.38 (0.36-5.21)	0.64 (0.24-1.70)	0.90 (0.30-2.67)	0.81 (0.26-2.55)
Hosmer & Lemeshow p for goodness of fit	0.23	0.19	0.27	0.29
CI = confidence interval; OR = odds ratio				

Table 8.8c shows that, in contrast to the results presented in table 8.7a where it was shown that exposure to allopurinol alone does not influence risk of experiencing an incident vascular event, in the presence of all the combinations of medications used to treat vascular risk factors (except the combination of anti-hypertensive medications with lipid-lowering medications) those who had ever been exposed to allopurinol were less likely to experience an incident vascular event than those who had never been. This suggests that there may be a role for combination therapy in the prevention of vascular events in gout patients, using both treatments for vascular risk factors and allopurinol.

8.8 Strengths and limitations of this study

8.8.1 Strengths

This study has several strengths. It uses a matched design to reduce the influence of socio-economic confounders that may bias the estimate of effect size, and uses a multivariable model to investigate the effect of other potential confounders on the relationships of interest between exposures to medications and odds of incident vascular event.

The use of primary care EHR means that reliable data on prescribed medications was available for a long period of time, preceding the diagnosis of gout (or matched index date for controls) where the cohort study time begins. This allows assessment of cumulative exposure to these drugs in order to compare these findings with those from the multilevel discrete-time event history analysis (MDtEHA) whereby exposure was measured per one year of follow-up and did not

include any exposure prior to the study. Furthermore the use of DDD in calculating exposure allowed direct comparison of the effect of different groups of medications on odds of vascular event, which is not otherwise possible. This is the first study to examine the effect of exposure to these medications on risk of all vascular events in patients with gout, and to use DDD in order to facilitate inter-group comparison. This study is also the first to investigate the temporal relationship of the most recent prescription for the medications of interest to odds of first vascular event. This is also the first study to quantify the effect of time since last prescription of the drugs of interest on the risk of a vascular event, which is important since it informs clinical decisions about the optimum prescribing patterns for each individual drugs to reduce vascular risk, and also the peaks and troughs of risk relating to these prescriptions identifying key points at which to target surveillance for vascular events.

8.8.2 Limitations

This study was not without its limitations and these are described below

Data source

The limitations of conducting epidemiological research using primary care EHR such as those used in this study has previously been discussed in section 7.5.1 however one added limitation of this particular study was that it was a nested case-control study where cases and controls could only be selected from an existing sample population. This limited the number of cases and controls available for inclusion, although in case-control studies additional efficiency is not

necessarily added by increased numbers of cases and controls, since if matching variables are related to exposures of interest, then the frequency of exposures in controls can be distorted towards that of the cases, introducing selection bias. (Rothman & Greenland, 1998)

Study design

The case-control design is susceptible to information bias, which is systematic inaccuracy in the estimate of effect size resulting from differences in the type of data collected, or the methods of data collection within the study. This can also be present in studies using EHR if the records of those who have the outcome of interest are searched more thoroughly for the exposures of interest. Although every attempt was made to avoid this by searching the records of cases and controls using the same lists of codes to identify medications, the possibility of this cannot be completely eliminated.

Furthermore, the requirement for matching on age, gender and registered general practice to adjust for socio-economic confounders, and the nesting of the case-control study within the existing cohort population limited the number of potential participants for inclusion, and resulted in a ratio of 1:1 matching, which for reasons described in section 4.4.2 may reduce the power of the study to detect a true association. However, matching within case-control studies can also introduce selection bias if the matching criteria are related to the exposure, since the purpose of using controls is to estimate the distribution of the exposure in the source population and if controls are matched to cases on a factor correlated with the exposure then the frequency of exposure in the controls may be distorted towards that of the cases. This selection bias behaves like confounding and may

influence the effect estimate, usually towards the null, although this bias can be minimised by controlling for the matching variables in the analysis, as was the case in this study. (Rothman & Greenland, 1998)

Confounding by indication

As mention in section 7.5.1 confounding by indication is a potential problem in all observational studies, including those of a case-control design, resulting from the effect of prognostic factors on treatment decisions and producing a biased estimate of the treatment's effect on the outcome of interest. It is possible that participants in this study with the most severe disease are also those most likely to receive treatment, but also more likely to experience complications or poorer outcomes. The results whereby treatments look harmful, when in fact they are not, may simply reflect treatments being offered to those with the poorest prognosis and not as a result of the treatment itself.

Identification of exposures

Exposure to medications and covariates of interest was determined using lists of codes identified from the browser supplied by the CPRD. Whilst every effort was made to ensure that these lists were as comprehensive as possible, including attempting to identify validated lists of codes from existing literature, and in the absence of these by searching each chapter of the CPRD code browser relating to the organ system of interest individually to ensure that only the most specific and appropriate codes were included, it is possible that they were not exhaustive, introducing the possibility of an inaccurate estimate of effect size. Furthermore, as in the cohort study identification of the covariates of interest, e.g. hypertension rely on the accurate and consistent coding of these conditions in the EHR by GPs,

which although is thought to have high validity in the CPRD, cannot be guaranteed. However this is unlikely to differ between cases and controls groups and therefore is not likely to explain the study findings.

In addition, the EHR includes only prescribed medications. In the case of several NSAIDs (e.g. ibuprofen or diclofenac) and aspirin these medications are available to purchase over the counter, and therefore cumulative exposure to these drugs may have been underestimated, although this would be similar for those who experienced an event of interest and those who did not.

Exposure to some of the drugs of interest, particularly uricosurics and colchicine was rare, and the smaller numbers may not have been enough to detect any influence on odds of experiencing a first vascular event.

8.9 Summary

This chapter has presented a nested case-control study and the effect of exposure to medications used to treat gout and vascular risk factors on likelihood of first vascular event.

Exposure to allopurinol at any time relative to vascular event, or in any cumulative amount did not influence likelihood of vascular event. Participants who were exposed to colchicine more than 5 years ago were more likely to experience a vascular event as were those with above median cumulative exposure. In contrast, those with above average exposure to NSAIDs were less likely to experience a vascular event than those who were not exposed.

Participants who had been exposed to anti-platelet, anti-hypertensive and lipid-lowering medications within 2 years were more likely to experience a vascular event, odds of experiencing a vascular event increased with above median exposure to anti-platelet and lipid-lowering medications compared with below median or no exposure. In contrast, those with above median exposure were less likely to experience a vascular event compared with those with below median exposure, but was increased compared with those with no exposure.

Chapter 9: Discussion

9.1 Overview

This chapter will discuss the findings of the cohort study and their potential implications for clinical practice

9.2 Association of gout and vascular disease

This study provides evidence that gout is an independent risk factor for all vascular events, all cardiovascular events and incident peripheral vascular disease in men, and all vascular events with the exception of MI and all cerebrovascular events in female gout patients, in this cohort of primary care gout patients over the age of 50. The trend in the magnitude of this risk was found to be greater in women and increased over time.

The precise mechanism underlying the association between gout and vascular disease reported in this study remains unclear, but although risk is attenuated after accounting for the full range of traditional risk factors (age, gender, gout*gender interaction, smoking and alcohol exposure, BMI, Charlson co-morbidity score, history of hypertension, hyperlipidaemia, renal disease, exposure to prescription of aspirin or statins), excess risk of all vascular events, all cardiovascular events and PVD persists in both genders, and excess risk of angina, CVA and TIA also persists in women.

The results of this study highlight many differences in the associations between gout and different types of vascular disease. These include differences in strength and significance of the associations between different types of vascular disease,

and effects of gender and risk of vascular disease over time. These will be discussed in the context of existing literature.

9.2.1 Association of gout and cardiovascular disease

Previous studies examining this association have been conflicting; however, this may arise from the heterogeneity of ascertainment of gout, geographical location, study population (health professionals, patients managed in primary and secondary care) and study sample size and gender distribution used. This study aimed to estimate the excess risk of vascular disease in a typical gout patient, which in the UK is managed in primary care, includes both men and women and is over the age of 50 at diagnosis of gout. Patients with a prior history of vascular disease were excluded in order to minimise the effect of surveillance bias on the estimate of risk. To our knowledge this is the largest study undertaken in primary care to examine this association to date.

Investigating these associations in primary care, where the majority of gout patients are managed, is important since many of the large prospective studies examining these associations (such as the Framingham study, (Abbott et al, 1988) Multiple Risk Factor Intervention Trial (MR-FIT), (Krishnan et al, 2008) and the Health Professionals Follow-up Study, (Choi & Curhan, 2007)) either recruit from secondary care, more specialised populations such as health professionals, or have other more restrictive recruitment criteria which limits their generalisability.

Previous studies examining the association between gout and cardiovascular disease have been conflicting; after adjustment for vascular risk factors results

from the Framingham study reported an increased incidence of CHD and angina in men but not women, although the number of women in their gout population was small (n=19/111 17%). (Abbott et al, 1988) Furthermore, the Framingham study design required participants to attend biennially for cardiovascular assessment, which despite facilitating accurate determination of risk factors, potentially introduced surveillance bias if awareness of these risk factors prompted patients to modify their lifestyle in order to mitigate against the onset of vascular disease. However, both a prospective study using a population of male health professionals from the US, and a primary care case-control study using gout patients of both genders from the Netherlands reported no increased incidence of CHD. (Gelber et al, 1997; Janssens et al, 2003)

Studies of the association between gout and MI produce similar conflicting reports with the findings of two studies in agreement with the results of this study; Krishnan et al, 2006, reporting an increased incidence of non-fatal and all MI in a male study population and Choi and Curhan, 2007, reporting an increased risk of non-fatal MI in men. (Choi & Curhan, 2007; Krishnan et al, 2006) Increased risk of non-fatal and all MI, (Kuo et al, 2013) and increased risk of all MI, (Seminog & Goldacre, 2013) have both been reported in samples of mixed gender, but the results are adjusted for, but not presented by, gender making direct comparison with these findings difficult. However, DeVera et al, 2010, reported an increased incidence of non-fatal and all MI in women but not men in a retrospective cohort study in Canada, whilst Abbott et al, 1988, report no association between gout and MI in either gender. (Abbott et al, 1988; De Vera et al, 2010) DeVera et al, 2010, used a similar sized population of gout patients to our sample (9642), however their participants were recruited from an older age (over 65 years) and included

those managed in primary and secondary care. (De Vera et al, 2010) This may introduce the potential for confounding by disease severity since patients managed in secondary care represent the more severe end of the disease spectrum and are more likely to be at risk of complications of gout including vascular events. Furthermore the excess risk identified in this study may be explained by a number of lifestyle factors such as smoking, alcohol and BMI which they were unable to account for in their analyses, meaning that despite their known influence on vascular risk, the contribution of these risk factors to the estimate of risk in this study remained unmeasured. (De Vera et al, 2010) The results of this study suggest the excess risk of vascular disease in gout patients, although perhaps not of the same magnitude, is similar to that seen in other inflammatory arthritides, such as RA, with the greatest risk conferred in patients with established disease. (Aviña-Zubieta et al, 2008) Mechanisms such as accelerated atherosclerosis and auto-immune inflammatory pathways involving TNF-alpha, IL-1 and IL-6 are thought to be responsible for increased cardiovascular risk in other inflammatory arthritides, (Soltész et al, 2011) and are equally applicable in gout following activation of the inflammasome in response to MSU crystals, (Jin et al, 2012) with evidence of persistent inflammation between acute attacks. (Pascual et al, 1999; Roddy et al, 2013) In addition to this, hyperuricaemia has been shown to increase cardiovascular risk through endothelial dysfunction, renovascular disease, hypertension and direct pro-inflammatory effects on vascular cells. (Jin et al, 2012; Soltész et al, 2011) This mechanism will be discussed in more detail in section 9.3.

9.2.2 Gout and cerebrovascular disease

An increased risk of all cerebrovascular events, TIA and CVA was found in women, and increased risk of TIA found in men with gout after adjustment for the covariates in model 1. After adjustment for the wider range of covariates in model 2, the risk remained but was attenuated in women with gout and was not seen in men. The association between gout and incident cerebrovascular disease has not been extensively researched, and thus there is little existing literature with which to compare these results. A recently published paper reported an increased risk of subsequent stroke following gout requiring hospital admission in patients with no previous history of stroke. They report a rate ratio for all strokes of 1.71(1.68-1.75), ischaemic stroke 1.68 (1.64-1.73), haemorrhagic stroke 1.69 (1.61-1.77) and stroke of unspecified type of 2.00 (1.95-2.06). The associations were stronger in younger age groups and also stronger in women than men. (Seminog & Goldacre, 2013) However, the sample of gout patients used required hospital admission for their gout, which is not representative of the wider population of patients with gout, and introduces confounding by gout disease severity. Furthermore, no attempt was made to account for traditional vascular risk factors which are likely to have an important bearing on this relationship.

Teng et al, 2012, investigated mortality from fatal stroke in patients with gout, but no statistically significant associations were found in either gender, which would support the findings in male but not female participants of this study. (Teng et al, 2012)

These findings suggest that traditional vascular risk factors may be responsible for these increased risks in men, but that there are alternative factors influencing

these relationships in women. These will be discussed in more detail in section 9.5.

9.2.3 Gout and peripheral vascular disease

The association with peripheral vascular disease in both genders is also particularly strong. This supports the findings of the single study to have previously investigated this relationship. (Baker et al, 2007) Few studies have also linked hyperuricaemia with PVD. (Langlois et al, 2003; Shankar et al, 2008; Tseng, 2004; Vigna et al, 1992) This association may result from common risk factors shared by gout and PVD, such as hypertension and metabolic syndrome. (Shammas, 2007) It has also been suggested that tissue damage caused by hypoxia resulting from peripheral arterial disease leads to adenine nucleotide breakdown and increased production of uric acid. (Langlois et al, 2003)

9.3 Mechanisms underlying differing risk of vascular disease by site

This is the first study to date to examine associations with all three of these forms of vascular disease simultaneously allowing direct comparison. Having discussed the associations between gout and different forms of vascular disease in the context of existing literature, the reasons for the differences between these associations will now be discussed.

Major risk factors for cardiovascular disease are also considered risk factors for cerebrovascular diseases and peripheral vascular disease. However, it has been reported that some risk factors are more strongly associated with particular forms

of vascular disease, for example hypertension is the most significant risk factor for cerebrovascular disease, (O'Donnell et al, 2010) hyperlipidaemia for coronary heart disease and smoking and diabetes for PVD. (Fowkes et al, 2013) Data from the Framingham study were used to develop individual calculators, which used combinations of the risk factors most strongly associated with each type of vascular disease to estimate a patient's risk of coronary heart disease, stroke and PVD. (Murabito et al, 1997; Wilson et al, 1998; Wolf et al, 1991) These were later used to create a calculator of overall cardiovascular risk, although the authors acknowledge that this overall risk model does not perform as well as the individual calculators in estimating risk of particular diseases. (D'Agostino et al, 2008)

It is possible that excess risk associated with gout differs between vascular diseases at different sites because either hyperuricaemia, or the pro-inflammatory cytokines released in response to the presence of MSU crystals, preferentially predispose to cardiovascular and peripheral vascular disease as opposed to cerebrovascular disease, or interact more potently with other risk factors involved in cardio- or peripheral vascular disease pathogenesis rather than cerebrovascular disease.

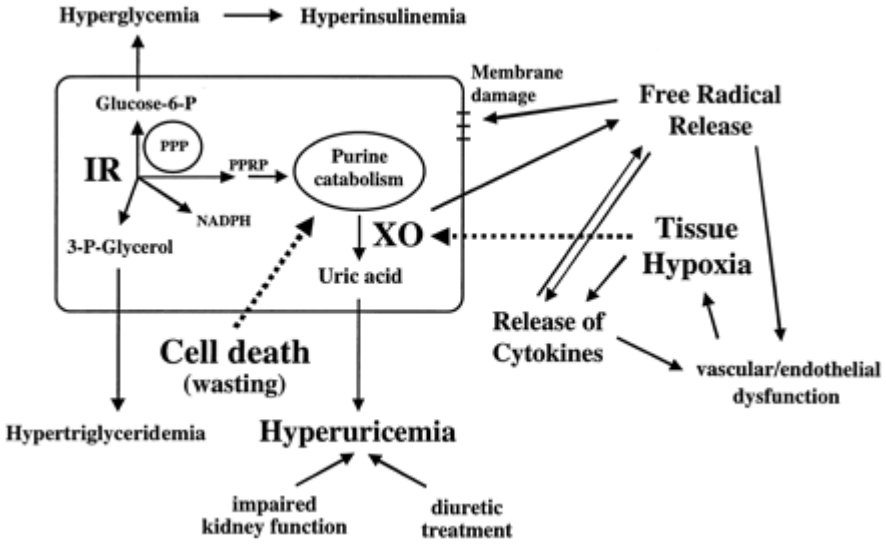
The reasons for the importance of particular vascular risk factors in the distribution of atherosclerosis across different vascular beds, e.g. plaques of the carotid endothelium rather than those of the coronary arteries, remain unclear. Some of the answers may lie in the mechanisms by which atherosclerosis predisposes to vascular disease, and the interaction of uric acid and the pro-inflammatory cytokines released as part of an MSU-induced inflammatory pathway. These

mechanisms include both decreased endothelium-dependent vasomotion and plaque deposition, and these will be discussed in turn.

As described in section 2.4.1 oxidative stress plays an important role in endothelium-dependent vasodilation, through reduction in the bioavailability and action of nitric oxide on vascular smooth muscle cells, and inhibition of platelet aggregation and expression of adhesion molecules, (Pennathur & Heinecke, 2007) resulting in a proatherogenic state. (Landmesser et al, 2006) The involvement of uric acid in this pathway is complex, since whilst uric acid is known to be an anti-oxidant, soluble uric acid can also react to form oxidants, increase lipid oxidation, upregulate the renin-angiotensin system and induce endothelial dysfunction through proinflammatory and proliferative effects on vascular smooth muscle cells. (Kanellis & Kang, 2005)

The relationship between the action of xanthine oxidase, hyperuricaemia and other contributors to vascular risk are presented in figure 9.1 below.

Figure 9.1 Role of hyperuricaemia in vascular risk



Source: (Anker et al, 2003)

Insulin resistance (IR) and cell death increase purine levels and thus stimulate increased action of xanthine oxidase (XO), which results in increased levels of uric acid but also production of free radicals which in turn promote release of inflammatory cytokines. Tissue hypoxia also stimulates increased action of XO, release of inflammatory cytokines and further perpetuation of vascular dysfunction. (Anker et al, 2003) The contribution of the action of XO and uric acid therefore seems to be most directly linked to endothelial dysfunction which would suggest that gout should predispose to forms of vascular disease where endothelial dysfunction is most important in its pathogenesis or manifests clinical symptoms early in its course prior to plaque deposition. This same theory has been applied to explain the relationship between smoking and vascular disease, as it is known that smoking predisposes to vascular disease by its systemic pro-thrombotic effect, and smoking is a stronger risk factor in cardiovascular and peripheral vascular disease, than cerebrovascular disease. It may be that this pro-thrombotic effect is more important than plaque formation in the development and progression of cardiovascular and peripheral vascular diseases, but plaque rupture and thrombosis are most strongly associated with acute events such as CVA and MI, rather than stable angina or peripheral vascular disease and so the relationship is likely to be more complex. Endothelial dysfunction is common to the pathogenesis of all types and stages of vascular disease, and it seems likely that the pro-thrombotic effect of smoking interacts to accelerate the progression of atherosclerotic disease. This may also be the case with hyperuricaemia and gout whereby the increased action of XO combined with the high levels of circulating pro-inflammatory cytokines accelerate progression from endothelial dysfunction to

plaque deposition and instability through their cumulative contribution to oxidative stress.

Whilst it is possible that different risk factors predispose to plaque deposition compared to endothelial dysfunction, it is also possible that the relative importance of these two mechanisms may differ between vascular beds. For example, if atherogenesis is more important than endothelial dysfunction in the pathogenesis of coronary artery disease, then it is likely that factors which strongly predispose to atherogenesis are more likely to predispose to coronary artery disease. Selzer et al, 2004, showed that in women with systemic lupus erythematosus (SLE), traditional vascular risks and raised CRP predisposed more to atherogenesis, whereas whilst these factors also contributed to decreased arterial compliance, some SLE-specific characteristics such as low white cell count and high C3 levels also played an important role in increased vascular stiffness. (Selzer et al, 2004) It may be that a similar interaction between hyperuricaemia, and or pro-inflammatory cytokines released as part of MSU-driven inflammation, and traditional vascular risk factors such as hyperlipidaemia may predispose particularly to deposition in the coronary arteries and peripheral arteries rather than the carotid endothelium.

Perhaps the biggest risk factor for coronary heart disease is dyslipidaemia, a common co-morbidity in patients with gout. (Annemans et al, 2008) A recent review suggested that the relationship between lipids and cardiovascular disease is different in patients with rheumatoid arthritis, as presence of a proinflammatory state as a result of this condition reduces total cholesterol as well as HDL and LDL cholesterol levels in these patients, and that anti-inflammatory therapies increase these levels to varying degrees. In addition, the resulting increase in lipid levels is

not associated with an increased number of cardiovascular events, and disease-modifying drugs used to treat RA, such as methotrexate, have been associated with a reduction in cardiovascular death and incidence of MI in patients with RA. (Gonzalez-Gay & Gonzalez-Juanatey, 2014; Steiner & Urowitz, 2009) This would support the relationship between disease activity and risk of vascular disease in inflammatory conditions, and would seem an area of interest for future research in gout.

The interaction of uric acid with low-density lipoprotein (LDL) can be pro-oxidant or anti-oxidant in a similar way to the role of uric acid in oxidative stress, with the direction of the effect dependent upon the oxidative state of the LDL. In the presence of un-oxidised LDL, uric acid will act as an antioxidant. However, in the presence of oxidised LDL, uric acid becomes a pro-oxidant, a transformation that is poorly understood. (Krishnan, 2010) Oxidised LDL is known to be an important predictor of atherosclerosis, mediating endothelial injury. (Ishigaki et al, 2009) Binding of LDL to the endothelium is thought to be part of the initiation of atherosclerosis, and expression of LDL binding molecules in the plaque potentiates its development, where these LDLs can be modified or aggregated. These modified LDLs chronically stimulate an inflammatory response, inducing the release of chemoattractants and adhesion molecules by the endothelium and vascular smooth muscle cells. (Bentzon et al, 2014) Patients with gout have been shown to have high levels of antibodies to oxidised LDL, and that the concentration of these antibodies was related to LDL particle size and HDL levels. (Jiang et al, 2014) Levels of oxidised LDL are positively correlated with levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and high sensitivity CRP, a marker of inflammation produced by the liver in response to IL-6, further suggesting that

MSU-induced inflammation in gout may be associated with increased levels of oxidised-LDL. (Jiang et al, 2014) Levels of oxidised LDL were not found to be correlated with serum uric acid levels, (Jiang et al, 2014) again supporting the hypothesis that as for RA, (Zhang et al, 2014) it is gout disease activity rather than cumulative exposure to hyperuricaemia or dyslipidaemia that is the more important factor in predisposition to atherosclerosis, which is itself considered an inflammatory condition. (Hansson, 2009) Evidence is emerging to support the link between total body urate load and risk of CHD, with presence of tophi shown to be associated with significant excess risk of cardiovascular mortality even after adjustment for baseline serum urate levels. (Perez-Ruiz et al, 2014)

The metabolic syndrome, described in section 2.5.2 is also a common co-morbidity in gout, and represents a cluster of vascular risk factors. It has been reported to be an important factor in the pathogenesis of cardiovascular disease in rheumatoid arthritis, (Gremese & Ferraccioli, 2011) resulting from the expression of adipokines by adipocytes and immune cells, which form an important link between inflammation and metabolism underpinning insulin resistance, further impairing endothelial function. (Deng & Scherer, 2010)

Gremese & Ferraccioli, 2011, argue that as post-mortem evidence from RA patients demonstrates the presence of more inflammation and unstable plaques in the arterial media, but less atherosclerosis than in age and gender matched controls dying from cardiovascular causes, with similar overall numbers of lesions and grades of stenosis, the mechanisms underlying cardiovascular mortality differ in RA patients. (Gremese & Ferraccioli, 2011) This would seem to support the importance of plaque instability and thus the role of thrombi in the association

between vascular disease and inflammatory arthritis, and perhaps the argument that the difference in risk of cardiovascular and peripheral vascular disease, and cerebrovascular disease in patients with gout relates to the relative importance of endothelial dysfunction, plaque deposition and thrombus formation in each of these conditions.

However, if this were the full explanation, one would expect to see a statistically significant increase in risk of MI which this study did not find in women, and only found in men after adjustment for the less extensive range of covariates in model 1. This may be explained by an increased risk of unheralded fatal MI which we were unable to identify since cause of death was not available in this dataset. Similar mechanisms have been reported in RA patients, in that they are thought to be at increased risk of silent MI and sudden death, compared with symptomatic angina, (Gabriel, 2008; Maradit-Kremers et al, 2005) and thus incident disease may go unrecognised in primary care which could also be the case in gout.

It is also possible the differences in risk between sites of vascular disease may not relate to a difference in underlying pathophysiology, but simply to the more reliable identification and general coding of incident cardiovascular disease compared with cerebrovascular disease.

9.4 Differences over follow-up time

The results of the cohort study when the follow-up time is limited to one, two and five years exposes differences not only in the strength and significance of associations between gout and different vascular diseases, but also how these risks vary over time.

In the unadjusted analysis, the general trend is one of increasing relative risk over time for all vascular events, and all cardiovascular events, and is similar for both genders. However, after adjustment for the full range of vascular risk factors this trend changes with risk of cerebrovascular disease (all CVD, CVA and TIA) and PVD greater in the short term (up to one or two years) in women, whilst risk of all CHD and angina was greater in the longer term (up to five or ten years). In men only risk of all CHD and PVD persisted and both were greater in the longer term.

The trend in incidence of vascular diseases in patients with gout over time has not previously been reported. However, the findings of increased risk of all cerebrovascular disease, CVA, TIA and PVD in women being greatest within one to two years of diagnosis of gout, whilst risk of cardiovascular disease is greatest five to ten years after diagnosis supports the theory that the mechanism underlying risk of vascular disease in gout may be different than those without an inflammatory condition and may also differ between vascular disease at different sites. The difference in risk of PVD over time between men and women, with women being at greatest risk immediately following diagnosis of gout and men at greatest risk in the longer term, also suggests different mechanisms underlying the same vascular disease between genders. These gender differences will be discussed in more detail in section 9.5.

The trend in increasing risk over time of the other vascular outcomes measured could be explained in a number of ways. It may be the result of cumulative exposure to vascular risk factors (such as duration of gout or duration of hyperuricaemia), the importance of plaque deposition later in the atherosclerotic process in the pathogenesis of these conditions, may represent participants with

smaller initial inflammatory burden, or simply reflect the effective use of treatments for gout leading to a reduction in cardiovascular risk. Further research is required to elucidate the contributions made by these differing potential explanations, although this is likely to be multi-factorial. The non-linear increase in the vascular outcomes which did demonstrate increased risk over time would support the multifactorial nature of this relationship. The observed decrease in risk in men between one and two years, and in women between two and five years following diagnosis of gout, followed by a similar or continued increase in risk thereafter, was consistent in all vascular events and all cardiovascular events. This pattern would seem to suggest a "threshold effect" whereby cumulative exposures to risk factors must reach a critical mass, or combine in a particular way, before the threshold at which increased risk of a particular event is reached. This threshold effect underpins the use of an S-shaped curve in logistic regression models used to predict risk, and suggests that the effect of a particular covariate on an individual's risk of a particular outcome is minimal for low levels of the covariate until a particular threshold is reached. The risk then rises rapidly and remains high once the level of the covariate gets large enough. (Kleinbaum & Klein, 2010) A similar "threshold effect" has been previously described in the effect of lipoproteins on mortality in the general population, whereby mortality in cardiovascular disease was not linearly related, and only increased in those participants with the highest quintile of serum cholesterol measurements. (Goldbourt et al, 1985)

9.5 Gender specific associations

Research into the epidemiology of gout in women remains relatively scarce; however our findings of increased risk of vascular disease in females are

consistent with those of two previous studies that included female participants. (De Vera et al, 2010; Teng et al, 2012)

The reasons for this increased risk remain unclear, but may result from prolonged exposure to hyperuricaemia prior to the onset of clinical gout since women have been observed to have lower mean serum urate levels and an older mean age at onset of gout when compared to men, (Chen et al, 2012; Harrold et al, 2006) and women have also been shown to be at a lower risk of developing gout at a given level of hyperuricaemia then men with a comparable level serum urate. (Bhole et al, 2010) Since the incidence of gout is higher in post-menopausal women, it has been suggested that oestrogen is an important influence, by means of an effect on renal excretion of urate. (Bhole et al, 2010; Hak et al, 2010) Following the menopause, not only do levels of oestrogen reduce, but the incidence of abdominal obesity and associated hyperinsulinaemia increase, further impairing the renal excretion of urate and increasing the inflammatory effect on the vascular endothelium. (Bhole et al, 2010) It has been suggested that the same metabolic factors considered to be traditional vascular risk factors play a more important role in women than men, (Chen et al, 2012) not simply resulting from an increased incidence, but perhaps reflecting a stronger multiplicative effect between hyperuricaemia and metabolic vascular risk factors resulting in a higher propensity of women to hyperuricaemia-induced microvascular damage. (Cipolli et al, 2012)

It is possible that in women, the sudden influx of pro-inflammatory cytokines associated with the incidence of MSU crystal-induced inflammatory arthritis which defines gout, following asymptomatic hyperuricaemia, either results in a pathogenic interaction with other vascular risk factors to accelerate the progress of

disease from incidence of endothelial dysfunction to symptomatic vascular event. Alternatively this sudden increase in pro-inflammatory cytokines may predispose to plaque destabilisation and thrombosis in existing asymptomatic disease. It is also possible that since endothelial dysfunction is known to be an early feature of vascular disease, (Bentzon et al, 2014) that this mechanism plays a more important role in the pathogenesis of these conditions in women than plaque formation.

A more complex relationship between hyperuricaemia and vascular risk factors in women than in men is one possible explanation for the gender differences in the findings of this study, however it is also possible that less aggressive screening for, and management of, both gout and vascular risk factors in female patients in primary care is responsible for the gender difference in these associations. It has been shown that in RA patients, delay in diagnosis of RA is likely to be longer in women, (Lard et al, 2001) and that men with RA are more likely to receive comprehensive cardiovascular assessment than women. (Monk et al, 2013) Further research is required in order to elucidate the nature and importance of these relationships in patients with gout.

9.6 Strength of association

The HR for development of vascular disease in this study is lower than that reported for other inflammatory diseases, although a variety of different estimates of risk and outcome measures are used. This makes direct comparison of the findings difficult since odds ratios cannot be directly compared with standardised incidence ratios, and measurement of cardiovascular outcomes which include

stroke may yield differing estimates of risk than those which specifically measure coronary heart disease or MI.

Patients with rheumatoid arthritis have been reported to have increased risk of incident CVD (RR 1.48 95%CI 1.36-1.62), MI (RR 1.68 95%CI 1.40-2.03), CVA (RR 1.41 95%CI 1.14-1.74) and heart failure (RR 1.87 95%CI 1.47-2.39) in a meta-analysis of observational studies. (Avina-Zubieta et al, 2012) The magnitude of increased risk found in women with gout in this study is not dissimilar to that conferred by RA where practice has already been altered to identify and manage the risk of cardiovascular disease. (Peters et al, 2010)

SLE has also been associated with an increased risk of incident cardiovascular events with estimates of between a two and three fold increase in risk compared to the general population (RR 2.66 (95%CI 2.16-3.16)), (Magder & Petri, 2012) (HR 2.26 (95%CI 1.45-3.52)). (Hak et al, 2009) However, despite the smaller magnitude of the risk of incident CVD conferred by gout compared to SLE, the majority of SLE patients (and participants included in research studies investigating its relationship with cardiovascular disease) are female, which would support this study's findings of increased risk in women. (Wade & Major, 2011)

The increased risk of vascular disease associated with other inflammatory conditions is likely to suggest a common pathway linking inflammatory disease and vascular risk. However, the smaller magnitude of increase in risk in gout compared to RA and SLE, for example, may reflect the earlier mean age of onset of both RA and SLE, and thus the effect of prolonged exposure to inflammatory cytokines thought to responsible for the additional risk.

Increased risk of stroke has been associated with ankylosing spondylitis, PMR, RA and SLE. (Zoller et al, 2012) This would support the findings of increased risk of stroke in the female participants in this study, although due to the use of generalised codes for recording cerebrovascular events, it was not possible to differentiate haemorrhagic from ischaemic stroke in this study. Despite their many shared risk factors, the findings may have been different had it been possible to investigate them separately in this study.

The magnitude of the increased risk of cerebrovascular events is greater in these other inflammatory conditions and it is possible that this is explained by the younger mean age of onset of conditions such as SLE, AS and RA when compared with gout, which results in a longer duration of exposure to systemic inflammation, thus increasing risk of cerebrovascular disease.

An increased prevalence of PVD has also been shown in patients with SLE, (Erdozain et al, 2014; June & Scalzi, 2013)

9.7 Multilevel Discrete Time Event History Analysis

To date, this approach has not been used to estimate the effect of changing covariates during follow-up, on the risk of vascular disease in patients with gout.

Similar to the continuous survival analysis model, this discrete-time model also demonstrates a significant interaction between gout and gender in the effect on the risk of an incident vascular event, and the direction of the association between gout and risk of vascular events, for both genders, is also similar.

Other risk factors that were associated with the risk of an incident vascular event were prescription of aspirin and statins, obesity and raised blood pressure measurement, all of which made an incident vascular event more likely across all participants (gout and no gout). Male participants and those with CKD (both with and without gout) were less likely to experience a first vascular event, and this is in keeping with evidence that gout is protective against vascular mortality in patients with CKD. (Kok et al, 2012) This relationship may reflect surveillance bias introduced following increased vigilance for vascular risk factors following a diagnosis of gout or CKD. However, given that both gout and renal disease individually increase vascular risk, (Foley et al, 1998) the mechanism underlying this observation requires further investigation. Similarly, patients who did not have a measurement of BMI or blood pressure were less likely to have a vascular event than those who had a normal measurement, suggesting that GPs are successfully identifying and measuring risk factors in those at greatest risk. However, there may also be an element of confounding by disease severity, since those with more severe disease are more likely to develop complications such as vascular disease, but are also more likely to have risk factors measured.

9.8 Gout-specific exposures and risk of vascular disease

Incident vascular events were more likely in patients with gout in whom there was poor surveillance of SUA, whilst those who consulted frequently for gout were less likely to have a first vascular event, highlighting the role of surveillance in reduction of vascular risk in gout patients.

Gout patients exposed to allopurinol were more likely to experience all vascular events, all cardiovascular events and angina, but not MI or cerebrovascular or

PVD. This finding is supported by a recent cohort study which demonstrated an increase in risk of vascular events in patients with gout with no prior history of vascular disease, of a similar magnitude to that reported here, although they were unable to adjust for some important confounding factors (e.g. BMI) in their analysis. (Kok et al, 2014) However, the findings of this study and that of Kok et al, 2014, contrast with the evidence reporting reduction in risk of cardiovascular events conferred by gout treatment with allopurinol using a “treat-to-target” approach, and aiming for suppression of urate below 360 micromol/litre. (Joo et al, 2014; Wei et al, 2011) They also contrast with evidence supporting cardiovascular benefit of allopurinol on blood pressure, left ventricular hypertrophy and exercise tolerance in chronic stable angina in non-gout patients. (Agarwal et al, 2013; Noman et al, 2010; Rekhraj et al, 2013; Szwejkowski et al, 2013) This may suggest that there are gout-specific factors which contribute to vascular risk that allopurinol is unable to mitigate against. This will be discussed in more detail in section 9.9.1

Those without a measurement of serum urate recorded within the 6 months before or after diagnosis of gout were more likely to experience a first vascular event, (all vascular events and all cerebrovascular events) whilst those with recorded hyperuricaemia (SUA >360micromol/litre) during the same time period were not. This suggests that surveillance of urate levels in general practice plays a role in reducing risk of vascular disease, even where urate lowering therapy is not prescribed. This may result from selection bias, whereby those patients likely to request urate monitoring are most engaged with reduction in the severity of their disease and therefore less likely to have a vascular event, or those GPs least likely to request urate monitoring are less aware of the role of hyperuricaemia and

gout in vascular risk. Little is known of influences on GP monitoring urate levels and understanding of the vascular sequelae of gout.

Those gout patients consulting their GP more frequently (for any reason) were more likely to experience a first vascular event, perhaps reflecting the increased risk of vascular disease also found associated with increasing Charlson score. Conversely, patients who consulted their GP more frequently for gout were less likely to experience a first vascular event, and yet if frequency of consultation for gout is considered a proxy for severity, one might expect repeated consultation to predict increased risk of a vascular event. One explanation could be that more frequent consultation for gout increases likelihood of initiation of ULT which, although not demonstrated in this study may, when used optimally, contribute to a reduction of vascular risk. It is also possible that this finding is simply a reflection of the effect of surveillance bias, whereby repeated consultation provides more scope for opportunistic intervention regarding vascular risk factors. Alternatively, it may be that those who consult for their gout are less likely to have a vascular event than those who do not resulting from sub-optimal self-management of inflammation associated with flares using over-the-counter NSAIDs or other analgesia, rather than prescribed NSAIDs or colchicine. Little is known of the characteristics of gout patients who self-manage and the difference in long term health outcomes from those who are managed by their GP.

9.9 Medications and risk of vascular disease

Given the increased risk of experiencing an incident vascular event associated with gout identified by this study and the findings that exposure to allopurinol made a vascular event more likely, this section will discuss the investigation of the effect

of medications used to treat gout and vascular risk factors, such as hypertension, on odds of a vascular event. Two separate approaches were used to investigate this association; multilevel discrete-time event history analysis to investigate the contemporaneous association between changing risk factors and medications following diagnosis of gout and a nested case-control study to investigate the association between cumulative exposure to and time since most recent prescription for medications of interest.

9.9.1 Drugs used in the management of gout

Allopurinol

The findings of this study did not support a reduction in the risk of vascular disease associated with the use of urate-lowering drugs, despite the increased risk of vascular disease in patients with gout identified in chapters 3 and 6, the evidence that hyperuricaemia is also a risk factor for vascular disease suggesting that it would be reasonable to expect that urate-lowering therapy would confer some protective benefit in those gout patients it is prescribed for, and as discussed in section 7.3.2 various cardiovascular benefits conferred by allopurinol in non-gout patients have been demonstrated. However, less than half of the gout group was prescribed allopurinol.

Exposure to allopurinol at any time, or in any cumulative amount did not predict any change in odds of an incident vascular event compared to those who were never exposed, nor did vascular risk differ with time since last exposure to allopurinol, i.e. those having taken allopurinol within 2 years are not more or less

likely to experience a vascular event than those who not received a prescription for allopurinol for more than 5 years.

The findings of this study are in line with those of a recent case-control study investigating the effect of allopurinol on risk of MI, which also found that allopurinol did not significantly influence this risk. (Grimaldi-Bensouda et al, 2014) Since allopurinol is the most commonly used urate-lowering therapy, (Annemans et al, 2008; Cea Soriano et al, 2011) it would seem that this lack of effect of allopurinol on vascular risk merits further investigation.

There are several explanations for the finding that allopurinol use does not influence the risk of vascular disease. The first is that since the mechanism of action of allopurinol is to inhibit xanthine oxidase reducing both serum urate levels and oxidative stress, prescribed dosage (which can vary by individual) must be titrated in order to adequately and consistently inhibit xanthine oxidase. Therefore prescribing behaviour and adequate allopurinol dosing may be an important contributory factor.

National and international guidance recommends a titration regime for allopurinol, starting at 100mg and increasing dose according to the effect on serum urate levels when measured regularly, to attain suppression of urate below a target level of 360mmol/l. (Jordan et al, 2007; Zhang et al, 2006a) It has been reported that titration of allopurinol in this way can reduce incidence of cardiovascular co-morbidities. (Joo et al, 2014) However, evidence would suggest that GPs are much more likely to prescribe a fixed dose of 300mg, with reports of as few as 2-4% of patients receiving a dose greater than 300mg, and less than 50% of patients on urate therapy achieving a serum urate of less than 360mmol/L. (Annemans et

al, 2008; Wei et al, 2011) Similarly, studies have found regular measurement of serum urate is rare with reports of any serum urate testing in less than 10% of patients. (Annemans et al, 2008) This was also seen in this study and due to lack of urate data, no significant conclusions can be drawn about the effectiveness of allopurinol prescribed in lowering urate levels. It may be that allopurinol dose may be more important than duration of therapy in conferring cardiovascular benefit, since data shows gout patients taking higher doses of allopurinol (≥300mg) are more likely to have adequately suppressed levels of SUA, and have lower cardiovascular risk than those on lower doses (≤100mg). (Wei et al, 2011) In addition it is “high dose” allopurinol that has been shown to reduce cardiovascular risk in non-gout groups, with at least two of the studies using doses of ≥600mg, (Erdogan et al, 2012; Noman et al, 2010) which were only prescribed for 1% of this study population, although this is in line with estimates from other studies. (Annemans et al, 2008) The use of cumulative exposure in this study, the product of dosage and duration of therapy, allowed comparison of the effect of a higher dose for a shorter time with lower doses for a longer time. This has not previously been investigated in patients with gout, although it has been examined in patients with congestive heart failure (CHF), (Struthers et al, 2002) which suggested that whilst long-term low-dose (<300mg) allopurinol was harmful to cardiovascular outcomes, long-term high-dose (>300mg) allopurinol was associated with reduced cardiovascular risk in patients with CHF. (Struthers et al, 2002) This study does not suggest that there is a difference between low dose allopurinol taken for a short time (lowest exposure) and high dose allopurinol taken for a longer period (highest exposure) in patients with gout implying that it is not cumulative exposure to allopurinol but rather the degree to which the action of XO or oxidative stress is

inhibited in each individual by the dose of allopurinol they receive that determines the effect on vascular risk.

Given evidence of ongoing suboptimal prescribing of allopurinol, (Kuo et al, 2014; Roddy et al, 2007) the findings of this study demonstrating that exposure to allopurinol does not influence odds of incident vascular disease may simply reflect inadequate suppression of xanthine oxidase resulting from inadequate dose titration. However, even in the highest quartiles of daily dose of allopurinol risk of vascular disease was unaffected suggesting that other factors may also be important.

Further to the theory that suboptimal prescribing of allopurinol may contribute to the lack of effect of urate lowering therapy on risk of vascular disease, there may be patient factors, such as co-morbidity or polypharmacy which predict allopurinol prescribing behaviour which, once identified, may be used to change practice. For example, the BNF carries a caution limiting prescription of allopurinol to 100mg or below in the presence of renal impairment, and thus it may be expected that presence of renal disease may reduce likelihood of receiving a prescription for allopurinol. (Joint Formulary Committee, 2013) However, little is known of factors influencing allopurinol prescription in primary care.

In addition, even in patients for whom allopurinol is prescribed in line with accepted best practice, measures of prescribing behaviour cannot take into account compliance of patients with prescribed medication. In other words, the lack of effect of allopurinol on likelihood of incident vascular disease may simply be due to the patient not taking the drug as prescribed. There is evidence to support this suggestion, with recent literature reporting that adherence and

persistence with urate lowering therapy is poor in patients with gout. (De Vera et al, 2014; Kuo et al, 2014) The findings presented in table 7.4, report increased medication possession ratio (i.e. the amount of days in a set period in which patients have a prescription for allopurinol) reduced the odds of experiencing a vascular event, suggesting a relationship between compliance with allopurinol and vascular risk.

It is also possible that these findings may simply reflect confounding by indication whereby patients with most severe gout are more likely to be prescribed allopurinol, and are more likely to be at greater risk of complications such as vascular disease than those with less severe gout. Where confounding by indication is present, the estimate of risk does not accurately reflect the effect of allopurinol on risk of vascular event, since it cannot account for differences in severity between the two groups.

Uricosurics

Patients in the lowest and highest quartiles of exposure to uricosurics were more likely to experience an incident vascular event. Their odds of a vascular event were almost four times that of those not exposed to uricosurics, more than that in any of the other classes of drugs investigated.

There is limited evidence that probenecid is positively inotropic, increasing myocardial contractility. (Koch et al, 2013) Other inotropes such as dopamine and dobutamine have been associated with arrhythmias, myocardial infarction and increased mortality in patients with decompensated heart failure, (Felker & O'Connor, 2001) and it could be reasonably suspected that a similar mechanism underlies the increased odds of vascular events in this group.

An alternative explanation for this finding may be confounding by indication, whereby similar to those prescribed allopurinol, prescription of uricosurics results from more severe gout and potentially increased risk of vascular disease.

There has been little investigation of the role of uricosurics in reducing vascular risk in gout or non-gout populations, as their role in the management of hyperuricaemia and gout has been largely superseded by that of xanthine oxidase inhibitors.

Furthermore, these findings must be interpreted with caution due to the small numbers of patients prescribed uricosurics within this study population.

Colchicine

Gout patients who had been prescribed colchicine more than 5 years ago were more likely to experience a vascular event, although there was no contemporaneous association between exposure to colchicine and increased odds of a vascular event identified in either the multilevel discrete time event history analysis, or the nested case-control study. Above median cumulative exposure to colchicine also made an incident vascular event more likely.

Existing literature has examined the effect of colchicine on risk of vascular events in patients with existing vascular disease, demonstrating effective secondary prevention of cardiovascular events in those with existing stable coronary disease. (Nidorf et al, 2013) The effect of colchicine on risk of cardiovascular disease in patients with gout has also been explored, but the primary outcome for the majority of studies is limited to myocardial infarction, and results are conflicting. Grimaldi-Bensouda et al, 2013, found no effect on risk of MI associated with use of

colchicine, which supports the findings of this study, whereas Crittenden et al, 2012, reported decreased prevalence of myocardial infarction in patients with gout, but did not examine other vascular outcomes. (Crittenden et al, 2012; Grimaldi-Bensouda et al, 2014)

The explanation for these findings may lie in the reasons underlying cumulative exposure to colchicine; those with below median cumulative exposure to colchicine may either be patients who had infrequent attacks for which they sought treatment and therefore a lower inflammatory burden contributing to their risk of a vascular event, whereas those with above median cumulative exposure may have had frequent flares treated with colchicine, or have been prescribed it for prophylaxis against acute flares during initiation of ULT, both of which may indicate more severe gout which is more likely to be associated with complications such as vascular disease.

However, similar to the findings for allopurinol, higher cumulative use of colchicine did not make an incident vascular event less likely which would suggest multiple contributory factors to increased vascular risk unlikely to be completely mitigated by one drug.

NSAIDs

Time since exposure to NSAIDs did not influence odds of experiencing a vascular event. However, the findings related to cumulative exposure to NSAIDs differed; the MDtEHA examining the cumulative exposure within each year-long window following diagnosis of gout reported increased odds of a vascular event associated with increased exposure, in line with current evidence in the general population, (Bhala et al, 2013) but the case-control study showed that those with above

median cumulative exposure to NSAIDs were less likely to experience a vascular event that those not exposed to NSAIDs. There is no existing literature on cardiovascular risk in patients with gout treated with NSAIDs with which to compare our findings, but in light of the individual associations of both NSAIDs and gout with increased risk of subsequent vascular event, further research is required to explore this.

This difference may arise from the time period over which the cumulative exposure is calculated, since it is cumulative exposure measured in the case-control study whilst only exposure per year-long time window is considered in the cohort study. Perhaps the difference is the result of surveillance bias whereby those who are prescribed the highest amounts of NSAIDs are those who consult most often, thereby presenting increased opportunity for health surveillance and optimisation preventing poorer vascular outcomes. Furthermore, since NSAIDs such as ibuprofen and diclofenac are available to buy over the counter those with the lowest exposures may simply be those who choose not to consult, allowing less opportunistic screening for or management of vascular risk factors.

This relationship may also result from confounding by indication whereby higher doses of NSAIDs are only prescribed to those with the lowest co-morbidity and the lowest risk of vascular event. Since renal disease is a relative contraindication to use of NSAIDs, those with least exposure to NSAIDs may well represent those with renal disease which itself is predisposes to vascular disease. The association of greater cumulative exposure to NSAIDs with reduced odds of vascular event may also relate to the use of NSAIDs as prophylaxis against acute attacks during the initiation of ULT or may reflect surveillance bias whereby

patients consulting GPs with frequent acute attacks or for titration of ULT also provide more opportunity for identification and management of vascular risk. However, this was not the case for colchicine, where those with above median cumulative exposure to colchicine had increased odds of vascular event.

9.9.2 Drugs used to treat vascular risk factors

Antihypertensives

Gout patients who had been prescribed anti-hypertensives had higher odds of experiencing an incident vascular event than those who had not, and those with above median exposure to anti-hypertensives were more likely to experience a vascular event than those unexposed, but this risk was less than in those who had below median exposure. It seems therefore that increased exposure to anti-hypertensives can attenuate some of the excess risk, but not all.

Recent evidence has highlighted the increased prevalence of gout in those with uncontrolled hypertension and at least one additional cardiovascular risk factor, with prevalence increasing with the addition of each additional risk factor. (Juraschek et al, 2013a) The prevalence ratio of gout in those with uncontrolled blood pressure (BP) and two additional cardiovascular risk factors compared to those without cardiovascular risk factors was reported to be 4.5 (95%CI 3.1-6.3), suggesting that patients with gout and hypertension are already at high vascular risk. (Juraschek et al, 2013a) It is likely that the addition of increased risk from hyperuricaemia and MSU crystal-induced inflammation combined with hypertension does further increase vascular risk, and that these results, whereby

those prescribed anti-hypertensives had increased odds of experiencing a vascular event simply reflects cumulative vascular risk, rather than there being a genuine association between the drugs themselves and vascular risk.

However, an alternative explanation may be that it is those that have poorly controlled blood pressure despite anti-hypertensive medications, or who have additional risk factors which both reduce the threshold for prescription of anti-hypertensives and increase vascular risk (e.g. diabetes or renal disease) who remain more likely to experience a first vascular event even in the presence of prescribed antihypertensives.

The role of hypertension in the pathogenesis of vascular disease is well acknowledged if still not completely clear. It has been suggested that hypertension predisposes to vascular disease as a result of damage to both the arterial structure and function resulting from increased arterial pressure, as well as interactions with dyslipidaemia. (Chobanian, 2002; Hollander, 1976) This sustained increased pressure is thought to stimulate production of endothelial adherence molecules and cytokines, increase adherence of reactive white blood cells and promote their penetration into the intima, increase proliferation of vascular smooth muscle and connective tissue, and reduce endothelial vasodilatation whilst promoting vasoconstriction. (Chobanian, 2002; Lembo et al, 1998) Gout and MSU-crystal induced inflammation share a number of these mechanisms responsible for a pro-atherogenic state in common with hypertension, and since hypertension is common co-morbidity in gout, (Annemans et al, 2008) it is not difficult to understand why patients with gout and hypertension are at increased risk of vascular disease. These results suggest that risk of experiencing

a vascular event reduces with increasing exposure to anti-hypertensives, although this risk cannot be completely attenuated, and this would support evidence that medications used as anti-hypertensives, particular those which act on the renin-angiotensin system (RAS) are able to positively influence the structural changes contributing to formation of atherosclerosis, most notably reversing endothelial dysfunction thereby slowing or reducing progression to renal and cardiovascular damage. (Ruilope et al, 2007) It has also been suggested that synergistic action between drugs which target the RAS and HMG Co-A Reductase inhibitors can improve both endothelial function and insulin sensitivity in patients with Type II diabetes suggesting that perhaps a combined approach to management of cardiovascular risk should be adopted in those at high risk. (Lee et al, 2014) However, the effect of this approach is yet to be reported in either the general population or those with inflammatory conditions.

This study demonstrates that although management of hypertension is important in reducing cardiovascular risk, exposure to these medications alone is not sufficient. The effect of early and optimum treatment of hypertension in order to increase cumulative exposure and minimise vascular damage resulting from uncontrolled hypertension in patients with gout warrants further investigation.

Antiplatelet medications

Gout patients who had been prescribed antiplatelet medications were more likely to experience an incident vascular event than those who had not, but their usage does not seem to reduce that risk in either the cohort or case-control study. The case-control study reports that participants who were most recently exposed to anti-platelet medications within 2 years were more likely to experience a vascular

event than unexposed participants, but most recent exposure outside of that time period did not make a vascular event more likely. Furthermore those participants with above median exposure were more likely to experience a vascular event than the unexposed, and this risk was greater than in those with below median exposure. It is possible that these findings simply reflect the appropriate prescription of anti-platelet medications for those at greatest risk of a vascular event since platelets play an important role in the pathogenesis of vascular disease, and thus anti-platelet drugs play an important role in the reduction of risk of vascular events through a variety of mechanisms.

Aspirin is the most commonly used and reduces platelet aggregation, oxidative stress, plasma coagulation and platelet-dependent inhibition of thrombin production, also contributing to the vascular protective effect. (Mehta, 2002; Patrono, 1994) Clopidogrel binds irreversibly to the receptors on the surface of platelets which are activated by the presence of pro-aggregatory substances, preventing activation of receptors which are required for strong platelet aggregation. (Clappers et al, 2007) Dipyridamole blocks cellular uptake of adenosine, increasing levels of free plasma adenosine converted to cAMP, which in increased levels within the platelet inhibits aggregation. (Behan & Storey, 2004)

However, thrombosis is only one component underlying the pathophysiology of vascular disease, with oxidative stress and atherosclerosis also contributing. Therefore, however effective anti-platelet drugs may be at attenuating the risk associated with the thrombotic component, there are other contributory factors which these drugs may not mitigate against.

Whilst in high doses aspirin is known to have a uricosuric effect, in lower doses used for cardiovascular protection, aspirin is thought to increase serum levels of urate by reducing renal excretion. (Caspi et al, 2000) Thus, it seems that exposure to aspirin may simply be a proxy marker for gout patients at high risk of vascular event, or alternatively, it may actually increase levels of hyperuricaemia thus increasing the vascular risk conferred, rather than reducing it.

There is currently no evidence examining the relationship between anti-platelet drugs, gout and vascular disease, but these findings may suggest that usual strategies for primary prevention of vascular disease can mitigate some of the excess risk associated with gout but not eliminate it.

Lipid-lowering medications

Statins have been shown to reduce all-cause mortality, cardiovascular mortality and major coronary events in the general population. (Naci et al, 2013) In this population, gout patients who had been prescribed lipid-lowering medication, which included fibrates and ezetimibe in addition to statins, were more likely to experience a first vascular event, although this likelihood reduced with increasing exposure with those taking the highest quartile of daily dose of lipid-lowering drugs having no increased risk of a vascular event, in the cohort study. The case-control study also demonstrates that patients with above median exposure to lipid-lowering drugs, although more likely to have a vascular event than those who were unexposed, were less likely to experience a vascular event than in those with below median exposure. This supports the importance of lipids in vascular risk in patients with gout, by predisposing to oxidative stress, endothelial dysfunction and

plaque deposition; together with effects on cytokine levels including IL-1, IL-6 and TNF. (Jiang et al, 2014)

This may also reflect appropriate prescription of lipid-lowering medications for those at greatest risk of vascular event. However, in contrast to the results of this study in patients with gout, in the general population lipid-lowering drugs have been shown to successfully reduce risk of vascular event. (Naci et al, 2013) This would imply that there is some other contributory or potentiating factor which makes lipid-lowering drugs less effective in patients with gout. In other inflammatory rheumatological conditions it has been suggested that this factor is chronic inflammation which interacts directly and indirectly with both traditional and novel vascular risk factors. (Choy & Sattar, 2009) It has been shown that treatment of rheumatoid arthritis can improve pro-atherogenic lipid abnormalities without the use of lipid-lowering medications. (Steiner & Urowitz, 2009) This would imply that cardiovascular risk associated with hyperlipidaemia in treated RA patients should be similarly reduced by the use of lipid-lowering medications to that in the general population.

This has not been investigated in patients with gout, but it is possible that a similar interaction between chronic inflammation in untreated or suboptimally managed gout and lipid structure and function exists, altering not only the ratio of cardioprotective HDL to pro-atherogenic LDL, but also changing the structure of these lipids and modifying their function by further impairing the cardioprotective effect of the remaining HDL, and potentiating the pro-atherogenic effects of LDL through oxidation. (Choy & Sattar, 2009) This may explain the temporal relationship of use of lipid-lowering medication and risk of vascular event, since

only most recent exposure within two years was found to be associated with increased odds of a first vascular event, whilst most recent exposure outside of two years (those who might be expected to be at greatest risk since lipid-lowering medication had been indicated and initiated but discontinued) was not associated with increased odds of a vascular event. If lipid profiles in patients with gout follow a similar pattern to those in RA then vascular risk due to hyperlipidaemia can be attenuated using lipid-lowering medications in those patients with adequate suppression of the inflammatory component, but not whilst inflammation persists. This chronic inflammation is likely to render the majority of patients with gout, not simply those in this study, at risk from pro-atherogenic lipid profiles against which lipid-lowering medications are ineffective given that management of gout is often suboptimal, (Cottrell et al, 2013; Kuo et al, 2014; Mikuls et al, 2005a; Roddy et al, 2007) and that even where ULT is offered persistence with it is poor. (De Vera et al, 2014; Kuo et al, 2014)

An alternative explanation is that use of HMG Co-A reductase inhibitors ("statins") has been associated with insulin resistance and increased risk of diabetes, both of which further increase vascular risk, (Lee et al, 2014) and are known to commonly co-exist in patients with gout, (Annemans et al, 2008) and it may be that patients with gout are particularly susceptible to these cumulative risks.

Whatever the explanation, the findings of this study suggest that use of lipid-lowering medications alone does not attenuate cardiovascular risk in patients with gout, and that further investigation of both the effect of chronic inflammation in gout on lipid profile, as well as the effect of optimum treatment of gout on cardiovascular outcomes is warranted.

9.9.3 Drug combinations

Similar to the results discussed in 9.9.2 whereby drugs used to treat cardiovascular risk factors do not, in isolation, completely eliminate vascular risk, combinations of these medications do not reduce the odds of experiencing a vascular event. However, in the presence of all the combinations examined, with the exception of anti-hypertensives with lipid-lowering medications, those participants exposed to allopurinol were less likely to experience an incident vascular event, whereas allopurinol in isolation did not reduce odds of a vascular event. It is likely that this finding reflects a synergistic effect between allopurinol and the medications used to reduce vascular risk factors. There is a growing body of evidence that combinations of medications which include aspirin, anti-hypertensives and statins taken as individual tablets, or in fixed-dose combination poly-pills, reduce relative risk of cardiovascular disease by 50-60% in high risk individuals, with this reduction increasing to 70-80% where lifestyle interventions are also optimised. (Yusuf et al, 2014) Given the evidence that allopurinol also has substantial cardiovascular benefits, particularly its effect on oxidative stress and endothelial dysfunction as discussed in section 9.9.1, it seems reasonable that the addition of allopurinol to these combinations should reduce the risk of a vascular event.

Although this particular investigation is limited by small sample size and the comparison between ever and never exposure to these drugs, these novel findings justify further and more detailed investigation of the principle of combination therapy in the management of gout and associated vascular risk. In other conditions which have been linked with increased risk of vascular disease, for

example diabetes, this approach has already been adopted into clinical practice. Patients with diabetes are automatically considered for the initiation of the medications used to treat vascular risk factors that were investigated in this study at diagnosis, with lower blood pressure targets and a lower threshold for commencing primary prevention of vascular disease. (National Collaborating Centre for Chronic Conditions, 2008b) The results of this study suggest that further investigation of the effect of early initiation of similar primary prevention strategies in combination with allopurinol following diagnosis of gout is warranted.

9.10 Clinical implications of these findings

Medications used to treat vascular risk factors do not reduce the risk of experiencing an incident vascular event in patients with gout as might be expected, or has been demonstrated in the general population. (Antithrombotic Trialists' Collaboration, 2002; Naci et al, 2013) This would suggest that alternative strategies should be investigated. It is possible that prescription of these medications results in patients feeling “protected” from vascular risk and thus not controlling lifestyle factors e.g. BMI or dietary intake of cholesterol as strictly as they might have, further increasing vascular risk. However, the results presented in table 8.8c whereby in the presence of medications used to treat vascular risk factors participants exposed to allopurinol are less likely to experience a vascular event, suggest that a combination approach to the management of vascular risk, which uses allopurinol in addition to the medications traditionally used to treat vascular risk factors should be considered in gout patients. Further research is needed to investigate the efficacy of such an approach.

Use of allopurinol alone in this study does not make an incident vascular event any more or less likely. As previously discussed, the pattern of prescribing of allopurinol in this study is sub-optimal with the most commonly prescribed dose of being 300mg and only 1% prescribed a dose in excess of 300mg. This sub-optimal use of allopurinol is no different to no use of allopurinol in terms of its effect on vascular risk, suggesting that current prescribing behaviours need to change.

Finally, since above median exposure to colchicine made a vascular event more likely, whilst above median exposure to NSAIDs made a vascular event less likely, the results of this study would suggest that NSAIDs should be preferentially considered for management of acute flares, and particularly as prophylaxis during initiation of urate-lowering therapy, in those at high vascular risk, although further research is required to investigate this in the absence of any head-to-head trials between NSAIDs and colchicine in the management of gout.

9.11 Summary

This chapter has discussed gout as an independent risk factor for incident vascular disease, particularly peripheral vascular disease. Female gout patients were at greatest risk, despite being the minority of gout patients, perhaps reflecting the importance of post-menopausal oestrogen deficiency in impairing renal excretion of urate, or less effective identification and management of both gout and vascular disease in women. The strongest association found was between gout and cardiovascular and peripheral vascular disease, both of which are most strongly associated with atherosclerosis, however evidence examining vascular risk in other inflammatory arthritides has indicated that plaque instability and

decreased arterial compliance are most strongly implicated in the pathogenesis of increased vascular risk in these conditions. The interaction between uric acid, pro-inflammatory cytokines and LDL-cholesterol in gout patients potentiating first endothelial dysfunction, followed by accelerated atherosclerosis and plaque instability was highlighted as the most likely mechanism underlying this association in gout patients. This multifactorial aetiology is supported by the inability of any of the drugs used to treat gout or vascular risk factors investigated to reduce the risk of an incident vascular event when used in isolation. However, in the presence of combinations of medications used to treat vascular risk factors, exposure to allopurinol reduced odds of a vascular event. More research is required to elucidate the exact nature of these relationships and the mechanisms underlying them.

Chapter 10: Contribution of this work

10.1 Overview

This chapter will summarise the importance and original findings highlighted in this thesis. The implications of this research for clinical practice will be discussed and further research questions identified as a result of this investigation will be presented.

10.2 Gout and risk of vascular disease

This is the first study to date to examine associations with all three of these forms of vascular disease simultaneously allowing direct comparison, and thus identifying a difference in risk between vascular beds, and between genders. The results of the main retrospective cohort analysis described in chapters 5 to 7 highlighted that

Men with gout were at increased risk of **all vascular** events, **all cardiovascular** events and **PVD**

Women with gout were at increased risk of **all vascular** events, **all cardiovascular** events, **angina**, **TIA**, **CVA** and **PVD**

To demonstrate the effect of these findings on existing knowledge of the incidence of coronary heart disease in patients with gout, these results were added to the meta-analysis of existing studies examining this relationship presented in Chapter 3. Both studies included in the previous meta-analysis used a male only gout population and since the results of this study are presented by gender (due to a significant gout*gender interaction) the results for all CHD events for men were

pooled. The study effect sizes and weights are presented in Table 10.1 and Table 10.2 and the Forest plots shown in Figure 10.1 and 10.2 below.

Table 10.1 Study effect sizes and weights in meta-analysis of crude results of studies examining the association between gout and incident coronary heart disease

Study	Hazard Ratio	95% CI	% Weight
Abbott et al, 1988	1.60	1.10-2.20	13.07
Gelber et al, 1997	0.85	0.40-1.81	3.05
Clarson et al, 2014	1.36	1.27-1.45	83.88
D + L pooled effect size	1.37	1.20-1.57	100.00
CI= confidence interval; D+L= DerSimonian and Laird			

I^2 = 14.2% which reflects no significant heterogeneity, and Cochran's Q test yielded p=0.31 also suggesting no significant heterogeneity.

Table 10.2 Study effect sizes and weights in meta-analysis of adjusted results of studies examining the association between gout and incident coronary heart disease

Study	Hazard Ratio	95% CI	% Weight
Abbott et al, 1988	1.60	1.10-2.50	32.43
Gelber et al, 1997	0.59	0.24-1.46	12.36
Clarson et al, 2014	1.08	1.01-1.15	55.22
D + L pooled effect size	1.14	0.80-1.63	100.00
CI= confidence interval; D+L= DerSimonian and Laird			

I^2 = 61.6% which reflects significant heterogeneity, but Cochran's Q test yielded p=0.07 suggesting no significant heterogeneity.

Figure 10.1 Meta-analysis of crude incidence of CHD updated to include the findings of this study

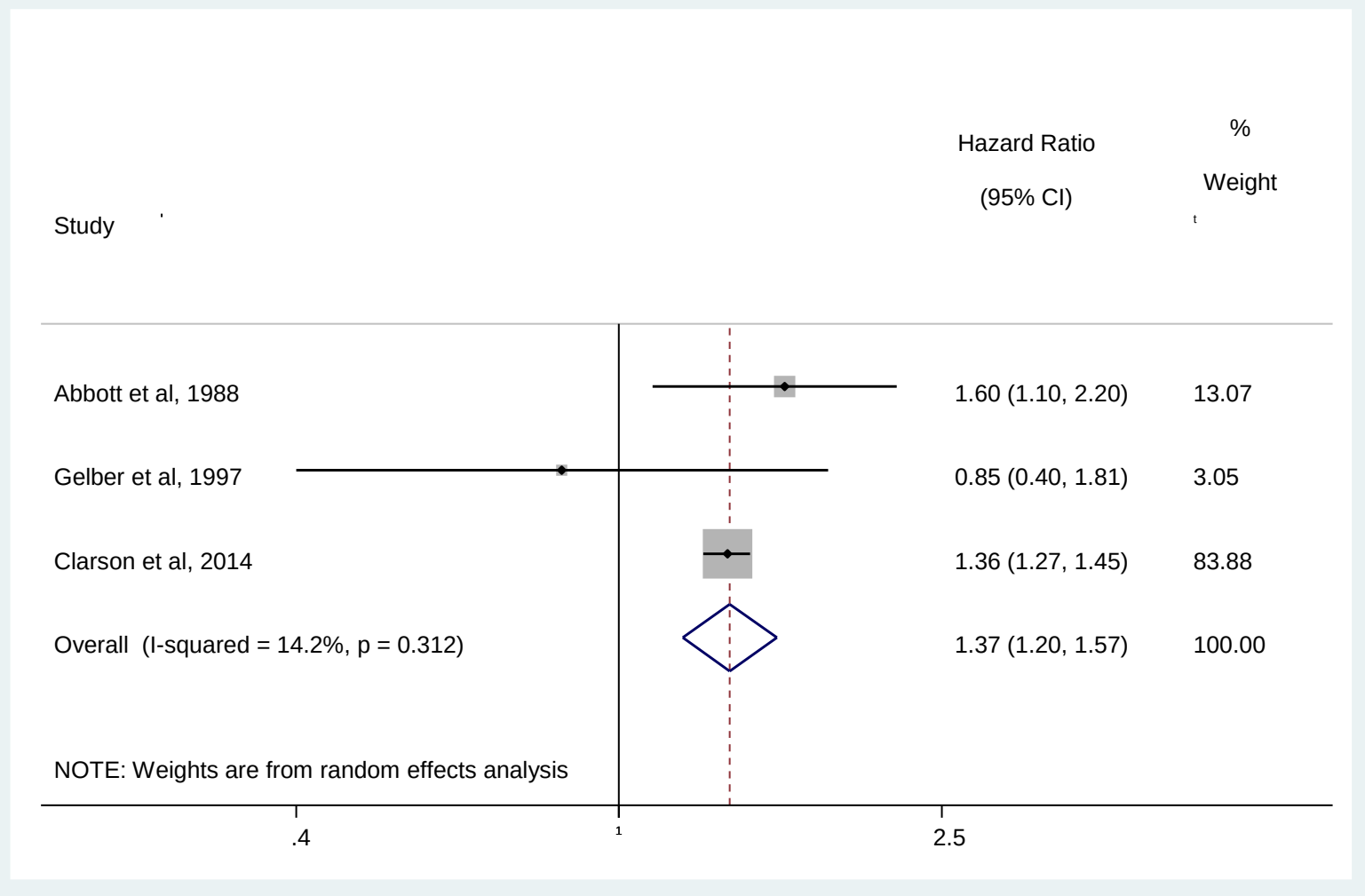
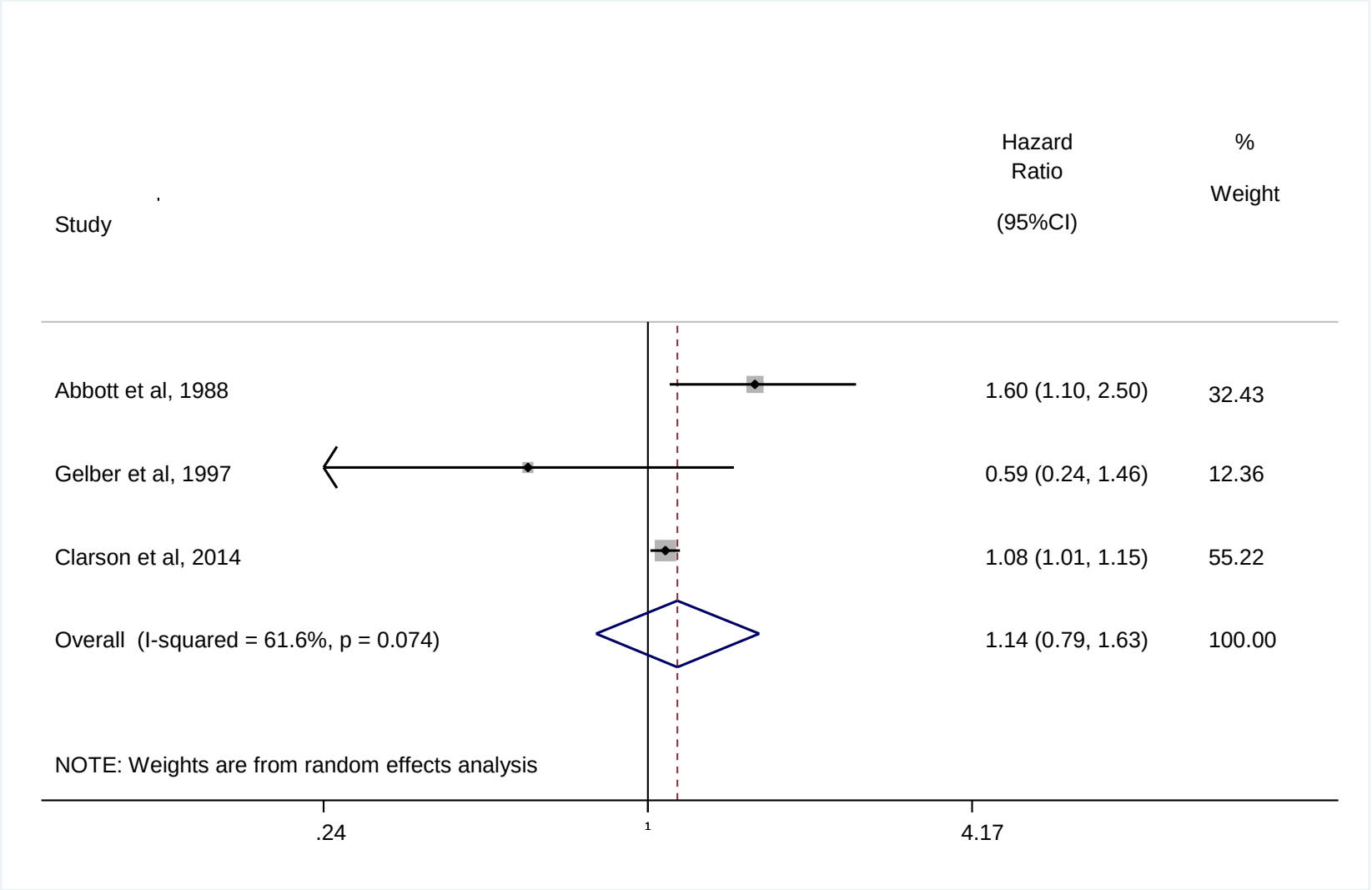


Figure 10.2 Meta-analysis of adjusted incidence of CHD updated to include the findings of this study



This study is the largest of the three to examine this relationship and alters the pooled estimate of risk of incident coronary heart disease in both crude and adjusted findings, and reduces the degree of between study heterogeneity. The pooled estimate of the crude incidence of CHD becomes statistically significant, whereas previously it was not, and demonstrates an increased risk of approximately 30% in patients with gout compared to those without. Although the pooled estimate of the adjusted risk did increase, it remained statistically non-significant, however, it should be noted that incidence of all CHD was only one outcome measured by this study, and the results presented estimating risk of cerebrovascular and peripheral vascular disease continue to point to an association between gout and vascular risk, even after adjustment for traditional vascular risk factors.

Major risk factors for vascular disease at one site e.g. coronary arteries had been thought to be equal risk factors at other vascular sites e.g. carotid and peripheral arteries, but this study demonstrates that gout predisposes most strongly to PVD, followed by CHD both of which are contributed to most strongly by atherosclerosis rather than thrombosis which is known to be preferentially associated with MI and CVA. It seems likely that the inflammation associated with gout interacts both directly and indirectly with other vascular risk factors to predispose most strongly to atherosclerotic vascular disease (cardiovascular and PVD) rather than to that where thrombus formation is the dominant causative factor (MI and stroke), although excess risk of stroke was found in women with gout after adjustment for multiple potential confounders.

By examining the risk of experiencing a first vascular event up to one, two, five and ten years following diagnosis of gout, excess risk of MI in men, and all

cerebrovascular events, CVA, TIA and PVD in women was found to be greatest in the first one or two years following diagnosis of gout, whereas excess risk of cardiovascular outcomes and PVD in men increases over time. The relationship of time following diagnosis of gout to excess vascular risk in patients with gout has not previously been reported. Furthermore the change in risk when follow-up is limited to one, two, five and ten years was not linear, with a reduction in excess risk in men between one and two years, and in women between two and five years, suggesting a "threshold effect" of contributory factors on the risk of experiencing a first vascular event.

Use of multilevel discrete-time event history analysis allows the effect of changes in these covariates during follow-up on overall odds of vascular event, in all participants to be investigated, and has not been used to investigate the relationship between gout and risk of vascular event. The use of this technique confirmed that men (gout and non-gout) were less likely to experience a vascular event than women. Participants (gout and non-gout) with CKD also had reduced odds of a vascular event. Exposure to gout, as well as raised blood pressure, obesity and prescription of aspirin and statins increased odds of an incident vascular event in both genders.

This is also the first study to investigate factors specific to gout patients which influence the risk of a vascular event, including prescription of allopurinol (found to predict increased likelihood of all vascular events, all cardiovascular events and angina), measurement of SUA (not having a record of SUA measurement predicted increased risk of a vascular event), number of GP consultations for any reason (as an indicator of consulting behaviour) and Charlson co-morbidity score (both of which increased likelihood of a vascular event as their values increased)

and number of consultations for gout (as a proxy for disease severity) which was found to reduce likelihood of all vascular events suggesting that disease surveillance may be important in helping to mitigate this risk.

The final original contribution of this research to the understanding of the relationship between gout and vascular disease is the investigation of the effect of drugs used to treat both acute and chronic gout and medications used to treat vascular risk factors on this association. Exposure to these drugs was calculated using DDD which allows comparison of the effect of different levels of exposure between groups of drugs. Cumulative exposure to each group of drugs per year following diagnosis of gout was calculated and analysed using MDtEHA (again a novel use of this technique). The advantage of using this technique was that it allowed exposure to change year by year and therefore the effect of dynamic exposure to medications such as those only likely to be taken occasionally (e.g. colchicine) to be estimated. The influence of cumulative exposure to the same groups of drugs was also investigated using a nested case-control design, which additionally examined the relationship between time since most recent prescription for these drugs and vascular event. This identified that taking allopurinol did not affect likelihood of a first vascular event, and above median exposure to colchicine made a vascular event more likely, whilst above median exposure to NSAIDs made a vascular event less likely, suggesting NSAIDs may be preferable in managing acute flares and as prophylaxis during initiation of urate-lowering therapy in patients at high vascular risk. Use of all medications used to treat vascular risk factors within 2 years made a first vascular event more likely, suggesting that current strategies used to manage CV risk reduction in the general population (which are mainly targeted at traditional CV risk factors such as

hypertension) are not sufficiently effective in patients with gout, perhaps reflecting the role of non-traditional risk factors such as inflammation and urate in the pathogenesis of vascular risk in gout. However of particular importance are the findings that in the presence of the drugs used to treat vascular risk factors, patients exposed to allopurinol were less likely to experience a vascular event. This suggests that perhaps a combination approach to the management of gout, and associated vascular risk, similar to that in diabetes, should be adopted, and that allopurinol should be considered an essential part of that risk reduction strategy.

The addition of the findings using different the different study methods have some important implications for clinical practice and these will now be discussed.

10.3 Implications for clinical practice

Evidence suggests that the burden of gout is rising, (Kuo et al, 2014; Robinson et al, 2013; Roddy & Doherty, 2010) and thus, at the population level, even a small increase in vascular risk will give rise to a substantial number of new vascular events. The results of this study demonstrate that although the absolute risk of vascular events per 1000 person years, even in the general population, is low, in women with gout the number of peripheral vascular events is more than doubled, and the total number of other cardiovascular (including angina but not MI) and cerebrovascular events (including CVA and TIA) are increased by half. The findings of this study suggest a need for important changes to clinical practice.

10.3.1 Screening for and identifying vascular diseases

There is evidence that cardiovascular in gout patients often goes unrecognised and under-treated in primary care. (Roddy et al, 2010) Only a quarter of people consulting with acute gout have screening for cardiovascular risk factors within the subsequent month, despite both national and international guidance recommending this. (Jordan et al, 2007; Khanna et al, 2012a; Zhang et al, 2006a) However, this study reports for the first time that in women, risk of cerebrovascular events and PVD is greatest in the two years following diagnosis of gout, suggesting that prompt intervention to reduce this risk should follow diagnosis of gout. The threshold effect in risk identified between one and two years in men and two and five years provides justification for regular and routine screening for vascular risk factors in patients with gout.

Furthermore, both gout and vascular disease have historically been considered diseases of men. However, these findings quite clearly show that this is not the case with the most notable increased risk of vascular disease in women, and thus, even in that minority of patients who are screened for vascular risk factors, those chosen may not be those most at risk. For this reason, both attitudes and practice must change with this new perspective on vascular risk to address both gout-specific and traditional vascular risk factors as a matter of priority in women with gout.

The association between gout and PVD reported in this study is a novel finding, and is the strongest of those identified. There is evidence which reports that 44% of patients screened for PVD had PVD without evidence of cardiovascular disease, (Hirsch et al, 2001) suggesting that this manifestation of systemic

atherosclerosis may not have been detected by routine practice in primary care, even by those adhering to current guidance. This highlights the need to consider screening for PVD in patients with a diagnosis of gout, not currently recognised as part of best practice, in addition to measuring traditional vascular risk factors.

Furthermore, recent evidence has highlighted the increased prevalence of gout in those with uncontrolled hypertension and at least one additional cardiovascular risk factor, with prevalence increasing with each additional risk factor. Prevalence ratio of gout in those with uncontrolled BP and two additional CV risk factors compared to those without CV risk factors was reported to be 4.5 (95%CI 3.1-6.3). (Juraschek et al, 2013a) This suggests that patients with gout, particularly women, should be included in "at risk" groups when public health measures aimed at reducing cardiovascular disease at a population level are being planned and resourced since treating cardiovascular disease costs the healthcare system in the UK approximately £8.6billion in 2009. (Townsend et al, 2012) Secondary care costs accounted for 64% of these costs, whilst primary care only 13%. If, by optimal identification and management of gout-specific and traditional vascular risk factors in patients with gout in primary care, it was possible to reduce the requirement for, and associated costs of, secondary care, then there are clearly financial gains to be made for the health economy, in addition to improved outcomes for patients.

10.3.2 Management of vascular risk factors in patients with gout

The results of this study point to disease activity and consequent inflammatory burden as important risks in gout that current vascular risk management strategies

are ineffective against. Therefore the management of vascular risk in patients with gout must include effective management of gout itself, similar to the approach taken in RA where it has been shown that optimum control of RA disease activity can correct pro-atherogenic lipid profiles associated with disease activity. (Steiner & Urowitz, 2009) Thus a change in practice to adopt a more aggressive approach to the use of medications, including newer agents, may be justified, with not only a lower threshold for initiation of medication, but consistent titration to achieve complete xanthine oxidase (XO) inhibition in order to reduce symptomatic burden of gout, associated inflammation and also its contribution to vascular risk through oxidative stress.

Traditional approaches to the reduction of cardiovascular risk appear less effective in patients with gout in this study than in the general population. Current guidance on primary prevention of cardiovascular disease has been amended to explicitly state that existing cardiovascular risk calculators do not perform accurately in estimating risk in patients with inflammatory disorders such as SLE and RA. This has led to the inclusion of RA as a risk factor in the QRISK2 cardiovascular risk calculator, (Hippisley-Cox et al, 2008) although the estimate of risk used in the risk equation is specific to RA and cannot necessarily be used to accurately estimate risk in other inflammatory conditions such as gout. This is important since primary prevention usually takes the form of treatment of traditional vascular risk factors such as hyperlipidaemia, but patients with high inflammatory burden and low LDL have been shown to have poorer survival than those with high LDL and low inflammatory burden, whilst currently unlikely to receive any primary prevention measures. Thus there will be a proportion of patients with inflammatory conditions, including gout, who are at unrecognised and untreated increased risk

of incident vascular disease, and a further proportion of patients with inflammatory conditions who are identified to be at increased risk of vascular disease using traditional measures, but in whom that risk is grossly underestimated. If this is not accounted for in tools widely used to estimate vascular risk and inform treatment decisions, clinicians will be unable to effectively estimate vascular risk in patients with inflammatory conditions, where a reduced threshold at which medications used to treat vascular risk factors should be initiated, or initiation as part of the routine management of inflammatory conditions following diagnosis may be of benefit.

In contrast, the findings whereby use of these medications within 2 years increased likelihood of vascular event compared with never having taken these medications may form the basis of an argument for discontinuing these drugs in some – however, it may also suggest that GPs are appropriately treating vascular risk factors in those most at risk without the ability to completely offset this risk. Perhaps the most important clinical implication of this study is that whilst in isolation, exposure to any of these medications did not reduce risk of vascular event, in the presence of medications used to treat vascular risk factors, those patients exposed to allopurinol are less likely to experience a vascular event. This is the first evidence to support a combination approach to the management of gout and associated vascular risk, similar to that adopted in diabetes, where allopurinol plays an essential role in synergistically reducing vascular risk in patients with gout.

10.3.3 Treatment of gout

Current evidence suggests that the clinical management of gout in primary care is suboptimal, (Kuo et al, 2014; Mikuls et al, 2005a; Roddy et al, 2007) and the burden of the condition is not to be underestimated with approximately 1 in 40 people in the UK, and over 8 million people in the US affected. (Kuo et al, 2014; Zhu et al, 2011) Only the minority of these receive ULT, and of those that do very few achieve adequate suppression of urate levels. (Annemans et al, 2008; Kuo et al, 2014) Prescribing of the higher doses of allopurinol that have been associated with cardiovascular benefit is extremely rare, (Annemans et al, 2008) and this was also the case in this study cohort, similarly measurement of serum urate was also infrequent suggesting that a treat-to-target approach to the titration of ULT was not in use, and in this study cohort not having serum urate recorded following diagnosis of gout predicted increased odds of vascular disease. Dosing of ULT required to achieve complete inhibition of XO and adequate suppression of SUA varies from one individual to another and the common practice of using fixed doses of allopurinol ≤300mg, (Annemans et al, 2008; Cottrell et al, 2013) is unlikely to be helpful in mitigating vascular risk. This is supported by the findings in this study that all levels of cumulative exposure to, and current use of allopurinol did not reduce odds of vascular event compared with no exposure to allopurinol within this cohort where indicators of optimal prescribing (regular measurement of serum urate to inform titration and prescription of doses in excess of 300mg) are only present in a small minority. As it has been demonstrated in patients with RA that a more aggressive management of the condition can reduce vascular risk, a similar aggressive approach to the management of gout by earlier initiation and

active titration to achieve target urate levels may be justified with the aim of reducing both symptomatic and vascular burden.

10.4 Future research questions

In reviewing the existing literature surrounding the relationship between gout and vascular disease it has become obvious that whilst much has been written about this association, there is actually a paucity of studies investigating it. Furthermore, the mechanisms underpinning this relationship are the subject of much discussion, but little research. The specific research questions identified that should be considered important for future patient care are described below.

10.4.1 Basic science research

The literature discussing the mechanisms underlying the pathophysiology of vascular risk at different sites has been presented in previous chapters, but most of this evidence comes from research into other inflammatory conditions, or extrapolation of hypotheses tested in the general population. There is little investigation of the mechanism responsible for excess vascular risk in gout, particularly gout in women. Of particular interest is the lipid profile in patients with gout, since reduction in HDL, LDL and total cholesterol in patients with RA has been demonstrated, increasing vascular risk. Whether patients with gout have a similarly abnormal lipid profile is not yet known, and particularly relevant to improving care of gout patients as it has been shown that in RA this abnormal lipid profile can be corrected by optimal control of the RA itself, without lipid-lowering

medication, and establishing the influence of optimal control of gout on lipid profile in gout patients may inform future guidelines on the management of gout.

It is likely that elucidating the interaction and relative importance of novel risk factors in gout in the pathogenesis of different forms, and at different stages of vascular disease may significantly inform clinical practice in optimally managing these risks, as it has in RA.

10.4.2 Epidemiological research

Prior to this study there had only been two previous investigations of the incidence of cardiovascular disease in patients with gout, and one study each of the incidence of cerebrovascular and peripheral vascular disease. Whilst the results of this study can be considered generalisable to a UK primary care population, further investigation of the incidence of cerebrovascular disease and peripheral vascular disease is warranted, and comparison between populations (e.g. New Zealand and Asia) would be valuable. It has previously been assumed that the risk of vascular disease increases over time, but there is little evidence to support this suggestion, and the findings of this study suggest that risk of some vascular outcomes are greatest in the first one or two years following diagnosis of gout particularly in women. If this is the case in other gout populations, this would support more aggressive management of gout, and routine primary prevention of vascular risk, required from diagnosis.

There is also much important epidemiological work required to elucidate how to manage this excess risk of vascular diseases most effectively in patients with gout,

since the findings of this study suggest that traditional methods are not wholly effective. Studies which are able to include serum urate levels or disease severity as covariates are scarce, and as such little is understood of the impact of optimal gout management on vascular risk.

Until the mechanisms by which patients with gout are at increased risk of vascular disease are further elucidated, clinicians will remain unable to optimally mitigate this risk. It is only by understanding the most important risk factors underpinning this association that an effective treatment strategy can be devised, without which gout patients will continue to experience potentially preventable health outcomes.

10.5 Peer-reviewed publications from this thesis

Two peer-reviewed publications have been published reporting the findings described in this thesis. These are:

Clarson LE, Chandratre P, Hider SL, Belcher J, Heneghan C, Roddy E, Mallen CD. Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis. European Journal of Preventive Cardiology. 2013: doi: 10.1177/2047487313514895 Published Online First 26 November 2013

Clarson LE, Hider SL, Belcher J, Heneghan C, Roddy E, Mallen CD. Increased risk of vascular disease associated with gout: a retrospective cohort study in the UK Clinical Practice Research Datalink. Annals of the Rheumatic Diseases. 2014: doi: 10.1136/annrheumdis-2014-205252 Published Online First 27 Aug 2014

Copies can be found in Appendix 3.

10.6 Summary

This section has discussed the findings of the retrospective matched-cohort study examining the association between gout and cardiovascular, cerebrovascular and peripheral vascular disease, in a cohort of primary care patients over the age of 50, with no prior history of vascular disease. Women are at greatest risk of vascular disease with the exception of MI, and all cerebrovascular events, and risk of peripheral vascular disease is greater than that of cardiovascular or cerebrovascular disease. Risk of peripheral vascular disease and cerebrovascular disease in women and angina in men is greatest in the one or two years following diagnosis of gout.

Reasons for these differences may include stronger predisposition to vascular disease at different sites associated with particular risk factors, or differences in the importance of endothelial dysfunction, plaque deposition and thrombosis in vascular disease at different sites and the risk factors which predispose to these. Inflammation and oxidative stress resulting from disease activity and inflammatory burden are likely to play a major role in excess risk of vascular disease in gout, in addition to the contribution of hyperuricaemia, and it is these gout-specific vascular risk factors which are difficult to mitigate against using traditional methods of vascular risk reduction.

Exposure to medications used to treat chronic gout, and colchicine do not alter the odds of vascular event, except with exposure to NSAIDs, where above median NSAID exposure made a vascular event less likely. Exposure to drugs used to mitigate against cardiovascular risk such as anti-hypertensives, anti-platelets and lipid-lowering drugs, was also associated with increased odds of vascular event,

although increasing dose exposure reduced odds in all three classes of drugs. Perhaps the most important finding is that whilst in isolation none of the drugs investigated (with the exception of the highest cumulative exposure to NSAIDs) made a vascular event less likely, however, in the presence of drugs used to treat vascular risk factors those participants exposed to allopurinol were less likely to experience a vascular event suggesting a role for combination therapy in managing gout and associated vascular risk.

In summary, the increased risk of vascular disease in gout is a complex multifactorial phenomenon that is still not well understood, and further research is required to find reliable ways to identify those patients with gout most likely to experience a vascular event and effective management strategies by which to reduce these risks.

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Appendix 1 – Search Strategies

Cardiovascular

Medline	Results	Embase	Results	CINAHL	Results
Exp MYOCARDIAL ISCHEMIA/	325758	Exp ISCHEMIC HEART DISEASE/	369641	Exp MYOCARDIAL ISCHEMIA/	39627
Exp CARDIOVASCULAR DISEASES/	1689301	Exp CORONARY ARTERY DISEASE/	175968	Exp CORONARY DISEASE/	21619
Exp CORONARY DISEASE/	167710	Exp CARDIOVASCULAR DISEASE/	2361569	Exp CARDIOVASCULAR DISEASES/	197801
(Heart and disease*).ti,ab	168855	(heart and disease*).ti,ab	199057	(heart and disease*).ti,ab	19806
(Coronary and disease*).ti,ab	119885	(coronary and disease*).ti,ab	142892	(coronary and disease*).ti,ab	13405
Chd.ti,ab	14100	Chd.ti,ab	17373	Chd.ti,ab	2295
Cardiovascular.ti,ab	222865	Cardiovascular.ti,ab	267075	Cardiovascular.ti,ab	29567
Angina.ti,ab	41023	Angina.ti,ab	47472	Angina.ti,ab	3061
Cvd.ti,ab	11723	Cvd.ti,ab	14529	Cvd.ti,ab	2279
Exp MYOCARDIAL INFARCTION/	134432	Exp HEART INFARCTION/	209176	Exp MYOCARDIAL INFARCTION/	19063
(myocardial and infarction).ti,ab	117481	(Myocardial and infarction).ti,ab	137618	(myocardial and infarction).ti,ab	12581
Exp ATHEROSCLEROSIS/	14946	Exp CORONARY ARTERY ATHEROSCLEROSIS/	14258	ATHEROSCLEROSIS/ (doesn't explode)	990
Atherosclero*.ti,ab	92930	Atherosclero*.ti,ab	108554	Atherosclero*.ti,ab	5922
(Heart and attack).ti,ab	7192	(Heart and attack*).ti,ab	8560	(heart and attack).ti,ab	1485
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1857949	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	2490265	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	216197

Cerebrovascular

Medline	Results	Embase	Results	CINAHL	Results
Exp CEREBROVASCULAR DISORDERS/	241225	Exp CEREBROVASCULAR DISORDERS/	340121	Exp CEREBROVASCULAR DISORDERS/	42315
(Stroke* or poststroke* or CVA*).ti,ab	121867	(Stroke* or poststroke* or CVA*).ti,ab	151706	(Stroke* or poststroke* or CVA*).ti,ab	27578
(cerebrovascular* or cerebral vascular).ti,ab	24900	(cerebrovascular* or cerebral vascular).ti,ab	29451	(cerebrovascular* or cerebral vascular).ti,ab	4281
(cerebral or cerebellar or brainstem or vertebrobasilar or brain).ti,ab	791101	(cerebral or cerebellar or brainstem or vertebrobasil* or brain).ti,ab	867926	(cerebral or cerebellar or brainstem or vertebrobasil* or brain).ti,ab	39990
(Infarct* or isch?emi* or thrombo* or apoplexy or emboli*).ti,ab	626489	(Infarct* or isch?emi* or thrombo* or apoplexy or emboli*).ti,ab	726532	(Infarct* or isch?emi* or thrombo* or apoplexy or emboli*).ti,ab	34599
4 AND 5	85549	4 AND 5	102629	4 AND 5	4198
(cerebral or intracerebral or intracranial or brain or brainstem or cerebellar or vertebrobasilar).ti,ab	836500	(cerebral or intracerebral or intracranial or brain or brainstem or cerebellar or vertebrobasil*).ti,ab	918036	(cerebral or intracerebral or intracranial or brain or brainstem or cerebellar or vertebrobasil*).ti,ab	42750
(haemorrhage* or hemorrhag* or haematoma or hematoma or bleed*).ti,ab	177576	(haemorrhage* or hemorrhag* or haematoma or hematoma or bleed*).ti,ab	308530	(haemorrhage* or hemorrhag* or haematoma or hematoma or bleed*).ti,ab	17842
7 AND 8	43218	7 AND 8	55090	7 AND 8	3634
(cerebrovascular ADJ accident).ti,ab	2690	(cerebrovascular ADJ accident).ti,ab	3299	(cerebrovascular ADJ accident).ti,ab	508
1 or 2 or 3 or 6 or 7 or 9 or 10	1010830	1 or 2 or 3 or 6 or 7 or 9 or 10	1150055	1 or 2 or 3 or 6 or 7 or 9 or 10	83059

Peripheral Vascular Disease

Medline	Results	Embase	Results	CINAHL	Results
Exp PERIPHERAL VASCULAR DISEASES/	40877	Exp PERIPHERAL VASCULAR DISEASE/	1034100	Exp PERIPHERAL VASCULAR DISEASES/	5529
Exp ARTERIOSCLEROSIS	114921	Exp ARTERIOSCLEROSIS/	155158	Exp ARTERIOSCLEROSIS/	10800
INTERMITTENT CLAUDICATION/ (doesn't exp)	6450	Exp INTERMITTENT CLAUDICATION/	7217	INTERMITTENT CLAUDICATION/	586
((peripheral ADJ vascular*) or atherosclerosis or arteriosclerosis or PVD or PAOD or PAD).ti,ab	104353	((peripheral ADJ vascular*) or atherosclerosis or arteriosclerosis or PVD or PAOD or PAD).ti,ab	120121	((peripheral ADJ vascular*) or atherosclerosis or arteriosclerosis or PVD or PAOD or PAD).ti,ab	6988
(arter* ADJ occlus*)	25696	(arter* ADJ occlus*)	29352	(arter* ADJ occlus*)	1618
(periph* ADJ arter*)	13340	(periph* ADJ arter*)	15856	(periph* ADJ arter*)	1462
(obstruct* ADJ arter*)	469	(obstruct* ADJ arter*)	497	(obstruct* ADJ arter*)	177
(claudica*)	7214	(claudica*)	8271	(claudica*)	634
(limb* ADJ isch?emi*)	4276	(limb* ADJ isch?emi*)	5224	(limb* ADJ isch?emi*)	54
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	241458	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	1079153	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	21563

Gout

Medline	Results	Embase	Results	CINAHL	Results
Exp GOUT/	8890	Exp GOUT/ (nothing below)	12085	GOUT/ (doesn't explode)	997
Gout*.ti,ab	8343	Gout*.ti,ab	9158	Gout*.ti,ab	762
OR	11228	OR	13858	OR	1139

Outcomes

Medline	Results	Embase	Results	CINAHL	Results
Exp INCIDENCE/	147723	Exp INCIDENCE/	207401	INCIDENCE/ (doesn't exp)	16622
Inciden*.ti,ab	499443	Inciden*.ti,ab	559518	Inciden*.ti,ab	48420
Exp PREVALENCE/	152963	Exp PREVALENCE/	277261	PREVALENCE/ (doesn't explode)	21503
Prevalen*.ti,ab	359636	Prevalen*.ti,ab	413497	Prevalen*.ti,ab	47943
Exp MORTALITY/	240944	Exp MORTALITY/	477207	Exp MORTALITY/	25261
Mortality.ti,ab	374929	Mortality.ti,ab	430657	Mortality.ti,ab	43611
Exp MORBIDITY/	305558	Exp MORBIDITY/	152262	Exp MORBIDITY/	39336
Morbid*.ti,ab	216898	Morbid*.ti,ab	258219	Morbid*.ti,ab	25152
OR	1442828	OR	1709643	OR	165606

Totals

Medline	Results	Embase	Results	CINAHL	Results
Cardiovascular AND gout AND outcomes	491	Cardiovascular AND gout AND outcomes	1251	Cardiovascular AND gout AND outcomes	34
		Limit HUMAN	1102		
Cerebrovascular and outcomes	93	Cerebrovascular AND gout AND outcomes	219	Cerebrovascular AND gout AND outcomes	5
Peripheral vascular AND gout AND outcomes	77	Peripheral vascular AND gout AND outcomes		Peripheral vascular AND gout AND outcomes	8

Appendix 2 – Read codes used to identify conditions of interest

Codes used to identify hypertension

CPRD Medcode	Read code	Read term
204	G2...00	Hypertensive disease
351	G20..11	High blood pressure
799	G20..00	Essential hypertension
1894	G201.00	Benign essential hypertension
2666	14A2.00	H/O: hypertension
3425	662O.00	On treatment for hypertension
3712	G20z.11	Hypertension NOS
4344	9N03.00	Seen in hypertension clinic
4372	G202.00	Systolic hypertension
4444	662..12	Hypertension monitoring
4668	G22..00	Hypertensive renal disease
5215	9OI..00	Hypertension monitoring admin.
5513	8HT5.00	Referral to hypertension clinic
7057	G2z..00	Hypertensive disease NOS
7329	G24..00	Secondary hypertension
8732	G2...11	BP - hypertensive disease
8857	G21z011	Cardiomegaly - hypertensive
10818	G20z.00	Essential hypertension NOS
10961	9h31.00	Excepted from hypertension qual indicators: Patient unsuit
10976	9h32.00	Excepted from hypertension qual indicators: Informed dissent
12680	8CR4.00	Hypertension clinical management plan
12948	662H.00	Hypertension treatm.stopped
13186	662P.00	Hypertension monitoring
13188	662G.00	Hypertensive treatm.changed
15106	G22z.00	Hypertensive renal disease NOS
15377	G200.00	Malignant essential hypertension
16059	G24z.00	Secondary hypertension NOS
16173	G21zz00	Hypertensive heart disease NOS
16292	G21..00	Hypertensive heart disease
16565	6627	Good hypertension control
18482	662c.00	Hypertension six month review
18590	662b.00	Moderate hypertension control
18765	G2y..00	Other specified hypertensive disease
19070	662d.00	Hypertension annual review
21826	662F.00	Hypertension treatm. started
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure

22333	8I3N.00	Hypertension treatment refused
24127	9OIA.11	Hypertension monitored
25371	G241000	Secondary benign renovascular hypertension
27511	6628	Poor hypertension control
27525	9OI..11	Hypertension clinic admin.
27634	9N1y200	Seen in hypertension clinic
28874	9OI8.00	Hypertens.monitor phone invite
29310	G22z.11	Renal hypertension
30776	6629	Hypertension:follow-up default
31117	9OI4.00	Hypertens.monitor.1st letter
31127	9OI5.00	Hypertens.monitor 2nd letter
31175	9OI6.00	Hypertens.monitor 3rd letter
31341	G24z100	Hypertension secondary to drug
31387	G24z000	Secondary renovascular hypertension NOS
31464	G21z.00	Hypertensive heart disease NOS
31755	G240.00	Secondary malignant hypertension
32423	G222.00	Hypertensive renal disease with renal failure
34744	G244.00	Hypertension secondary to endocrine disorders
36305	9OIA.00	Hypertension monitor.chck done
39649	G220.00	Malignant hypertensive renal disease
41634	9OI7.00	Hypertens.monitor verbal inv.
42229	G24zz00	Secondary hypertension NOS
43220	9OI2.00	Refuses hypertension monitor.
43935	G221.00	Benign hypertensive renal disease
45149	9OI1.00	Attends hypertension monitor.
50157	G210.00	Malignant hypertensive heart disease
51635	G241z00	Secondary benign hypertension NOS
52127	G211100	Benign hypertensive heart disease with CCF
52427	G211.00	Benign hypertensive heart disease
57288	G241.00	Secondary benign hypertension
57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
59383	G240000	Secondary malignant renovascular hypertension
69753	Gyu2.00	[X]Hypertensive diseases
73293	G240z00	Secondary malignant hypertension NOS
83473	G203.00	Diastolic hypertension
95334	G210000	Malignant hypertensive heart disease without CCF
97533	Gyu2100	[X]Hypertension secondary to other renal disorders
98230	67H8.00	Lifestyle advice regarding hypertension
99259	662q.00	Trial reduction of antihypertensive therapy

Codes used to identify hyperlipidaemia

CPRD Medcode	Read code	Read term
339	C320.00	Pure hypercholesterolaemia
340	9N0I.00	Seen in lipid clinic
637	C324.00	Hyperlipidaemia NOS
1173	C321.00	Pure hyperglyceridaemia
2091	9N0J.00	Seen in cholesterol clinic
2493	44P3.00	Serum cholesterol raised
3386	C320000	Familial hypercholesterolaemia
3484	C320.11	Familial hypercholesterolaemia
5791	C322.00	Mixed hyperlipidaemia
7447	C320z00	Pure hypercholesterolaemia NOS
9936	66X..00	Lipid disorder monitoring
10780	8B6A.00	Statin prophylaxis
10783	8BAG.00	Cholesterol reduction programme
10813	8I3C.00	Statin declined
10899	8BAG200	Cholesterol reduction program - declined
11529	8I76.00	Statin not tolerated
12111	8BL1.00	Patient on maximal tolerated lipid lowering therapy
12439	C321000	Hypertriglyceridaemia
12569	ZV65317	[V]Dietary surveillance in hypercholesterolaemia
13657	8HT1.00	Referral to lipid clinic
16085	1442	H/O: raised blood lipids
16306	C325.00	Lipoprotein deficiencies
16937	8B28.00	Lipid lowering therapy
26019	C320200	Hyperlipidaemia, group A
30335	9N4K.00	DNA - Did not attend cholesterol clinic
32244	8BG2.00	Lipid lowering therapy indicated
33694	ZC2CJ00	Dietary advice for hyperlipidaemia
34224	C320300	Low-density-lipoprotein-type (LDL) hyperlipoproteinaemia
34825	C320100	Hyperbetalipoproteinaemia
35720	44P4.00	Serum cholesterol very high
36806	9Oc..00	Lipid disorder monitoring administration
39147	8BAG000	Cholesterol reduction programme - invited
39699	C325000	High density lipoid deficiency
39849	8I3J.00	Lipid lowering therapy declined
51023	8BAG100	Cholesterol reduction program - attended
52992	C322.11	Fredrickson type IIb lipidaemia
53091	C320y00	Other specified pure hypercholesterolaemia
54499	C321.11	Fredrickson type IV lipidaemia
55855	C320.12	Fredrickson type IIa lipidaemia
59095	C320.13	Low density lipoproteinaemia
59564	C322.12	Fredrickson type III lipidaemia

66240	Cyu8D00	[X]Other hyperlipidaemia
69881	C323.12	Fredrickson type I lipaemia
71157	C327z00	Lipidoses NOS
71747	8CR3.00	Hyperlipidaemia clinical management plan
95952	C328.00	Dyslipidaemia
97166	9Oc0.00	Attends lipid disorder monitoring
97989	C320500	Familial defective apolipoprotein B-100
99032	9Oc3.00	Lipid disorder monitoring second letter
99456	C321.12	Very low density lipoprotinaemia

Codes used to identify chronic kidney disease

CPRD Medcode	Read code	Read term
350	K06..00	Renal failure unspecified
512	K05..00	Chronic renal failure
6712	K050.00	End stage renal failure
6774	14D..11	H/O: kidney disease
6842	K060.11	Impaired renal function
8330	K0D..00	End-stage renal disease
8919	K08..00	Impaired renal function disorder
9959	14D..12	H/O: renal disease
11787	K060.00	Renal impairment
12479	1Z13.00	Chronic kidney disease stage 4
12566	1Z12.00	Chronic kidney disease stage 3
12585	1Z14.00	Chronic kidney disease stage 5
12586	1Z11.00	Chronic kidney disease stage 2
12720	1Z1..00	Chronic renal impairment
19473	66i..00	Chronic kidney disease monitoring
25980	K08z.00	Impaired renal function disorder NOS
26001	4519	Deteriorating renal function
29013	1Z10.00	Chronic kidney disease stage 1
30735	6AA..00	Chronic kidney disease annual review
30739	9Ot0.00	Chronic kidney disease monitoring first letter
31549	7L1A.00	Compensation for renal failure
32423	G222.00	Hypertensive renal disease with renal failure
39840	K08y.00	Other impaired renal function disorder
41013	K08y300	Renal function impairment with growth failure
46626	9hE..00	Exception reporting: chronic kidney disease quality indicato
47342	Q48y000	Congenital renal failure
50804	K08yz00	Other impaired renal function disorder NOS
53852	K05..12	End stage renal failure
53940	Kyu2100	[X]Other chronic renal failure
61930	Kyu2.00	[X]Renal failure
64636	7L1Az00	Compensation for renal failure NOS
69679	9Ot4.00	Chronic kidney disease monitoring telephone invite
71271	9Ot..00	Chronic kidney disease monitoring administration
72962	9Ot1.00	Chronic kidney disease monitoring second letter
72964	9Ot2.00	Chronic kidney disease monitoring third letter
88494	9Ot3.00	Chronic kidney disease monitoring verbal invite
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
94965	1Z15.00	Chronic kidney disease stage 3A
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria

95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
95145	1Z1B.11	CKD stage 3 with proteinuria
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
95176	1Z1E.11	CKD stage 3A without proteinuria
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
95179	1Z16.00	Chronic kidney disease stage 3B
95180	1Z1F.11	CKD stage 3B with proteinuria
95188	1Z1C.11	CKD stage 3 without proteinuria
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
95422	9Ni9.00	Did not attend chronic kidney disease monitoring clinic
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
95571	1Z1D.11	CKD stage 3A with proteinuria
95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
97587	1Z1J.11	CKD stage 4 without proteinuria
97683	1Z1L.11	CKD stage 5 without proteinuria
97978	1Z1A.11	CKD stage 2 without proteinuria
97979	1Z19.11	CKD stage 2 with proteinuria
97980	1Z17.11	CKD stage 1 with proteinuria
99160	1Z1K.11	CKD stage 5 with proteinuria
99312	1Z1H.11	CKD stage 4 with proteinuria

Codes used to identify diabetes mellitus

CPRD Medcode	Read code	Readterm
506	C100112	Non-insulin dependent diabetes mellitus
608	66A2.00	Follow-up diabetic assessment
711	C10..00	Diabetes mellitus
758	C10F.00	Type 2 diabetes mellitus
1038	C100011	Insulin dependent diabetes mellitus
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
1549	C10E.00	Type 1 diabetes mellitus
1647	C108.00	Insulin dependent diabetes mellitus
1682	C101.00	Diabetes mellitus with ketoacidosis
1684	66A4.00	Diabetic on oral treatment
2378	66AJ.00	Diabetic - poor control
2379	9N1Q.00	Seen in diabetic clinic
2475	C104.11	Diabetic nephropathy
2478	66AJ100	Brittle diabetes
3550	66A..00	Diabetic monitoring
4513	C109.00	Non-insulin dependent diabetes mellitus
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
6125	66AS.00	Diabetic annual review
6430	9NM0.00	Attending diabetes clinic
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
6791	C108800	Insulin dependant diabetes mellitus - poor control
6813	1434.00	H/O: diabetes mellitus
7059	8H2J.00	Admit diabetic emergency
7563	66A3.00	Diabetic on diet only
7777	8H4F.00	Referral to diabetologist
7795	C106.12	Diabetes mellitus with neuropathy
8306	8H7f.00	Referral to diabetes nurse
8403	C109700	Non-insulin dependant diabetes mellitus - poor control
8414	8CA4100	Pt advised re diabetic diet
8836	66AR.00	Diabetes management plan given
8842	66A5.00	Diabetic on insulin
9013	66AJ.11	Unstable diabetes
9897	9OL..00	Diabetes monitoring admin.
10098	C10yy00	Other specified diabetes mellitus with other spec comps
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
10824	9N1i.00	Seen in diabetic foot clinic
10977	66Ac.00	Diabetic peripheral neuropathy screening
11041	9h41.00	Excepted from diabetes qual indicators: Patient unsuitable

11047	66AH000	Conversion to insulin
11094	9NND.00	Under care of diabetic foot screener
11348	9h42.00	Excepted from diabetes quality indicators: Informed dissent
11471	8B3l.00	Diabetes medication review
11551	C10B.00	Diabetes mellitus induced by steroids
11677	8H7r.00	Refer to diabetic foot screener
11848	C314.11	Renal diabetes
11930	9NN9.00	Under care of diabetes specialist nurse
12030	9OL6.00	Diabetes monitoring 3rd letter
12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
12225	8H7C.00	Refer, diabetic liaison nurse
12262	8I3X.00	Diabetic retinopathy screening refused
12307	66AU.00	Diabetes care by hospital only
12455	C10E.11	Type I diabetes mellitus
12507	9N2i.00	Seen by diabetic liaison nurse
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
12675	66AQ.00	Diabetes: shared care programme
12736	C10F500	Type 2 diabetes mellitus with gangrene
13071	66AI.00	Diabetic - good control
13078	13AC.00	Diabetic weight reducing diet
13191	9OL..11	Diabetes clinic administration
13192	9OLA.00	Diabetes monitor. check done
13194	9OL4.00	Diabetes monitoring 1st letter
13195	9OL5.00	Diabetes monitoring 2nd letter
13196	66AD.00	Fundoscopy - diabetic check
13197	9OL1.00	Attends diabetes monitoring
13279	C104y00	Other specified diabetes mellitus with renal complications
13597	42W1.00	Hb. A1C < 7% - good control
13604	42W3.00	Hb. A1C > 10% - bad control
14049	42WZ.00	Hb. A1C - diabetic control NOS
14050	42c..00	HbA1 - diabetic control
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
14889	C100111	Maturity onset diabetes
15690	C103.00	Diabetes mellitus with ketoacidotic coma
16230	C106.00	Diabetes mellitus with neurological manifestation
16490	66AH.00	Diabetic treatment changed
16491	C106.13	Diabetes mellitus with polyneuropathy
16502	C104.00	Diabetes mellitus with renal manifestation
17236	14P3.00	H/O: insulin therapy
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
17545	C108F11	Type I diabetes mellitus with diabetic cataract
17858	C108.12	Type 1 diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
17869	66AL.00	Diabetic-uncooperative patient

17886	66AM.00	Diabetic - follow-up default
18143	C109G11	Type II diabetes mellitus with arthropathy
18167	66AT.00	Annual diabetic blood test
18209	C109012	Type 2 diabetes mellitus with renal complications
18219	C109.13	Type II diabetes mellitus
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
18264	C109J12	Insulin treated Type II diabetes mellitus
18278	C109J00	Insulin treated Type 2 diabetes mellitus
18311	68A7.00	Diabetic retinopathy screening
18387	C10E700	Type 1 diabetes mellitus with retinopathy
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
18496	C10F600	Type 2 diabetes mellitus with retinopathy
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
18662	8HBH.00	Diabetic retinopathy 6 month review
18683	C10E500	Type 1 diabetes mellitus with ulcer
18766	212H.00	Diabetes resolved
18777	C10F000	Type 2 diabetes mellitus with renal complications
18824	8I3W.00	Diabetic foot examination declined
19381	8HTk.00	Referral to diabetic eye clinic
19739	68A9.00	Diabetic retinopathy screening offered
20900	9OLA.11	Diabetes monitored
21482	C102.00	Diabetes mellitus with hyperosmolar coma
21983	C108012	Type 1 diabetes mellitus with renal complications
22023	66AJz00	Diabetic - poor control NOS
22130	9OL3.00	Diabetes monitoring default
22487	C10N.00	Secondary diabetes mellitus
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
22823	66Ab.00	Diabetic foot examination
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
22884	C10F.11	Type II diabetes mellitus
24363	8A13.00	Diabetic stabilisation
24423	C108.13	Type I diabetes mellitus
24458	C109711	Type II diabetes mellitus - poor control
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
24836	C109C12	Type 2 diabetes mellitus with nephropathy
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
25627	C10F700	Type 2 diabetes mellitus - poor control
25636	66Aa.00	Diabetic diet - poor compliance

26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
26603	9OL2.00	Refuses diabetes monitoring
26604	66AY.00	Diabetic diet - good compliance
26605	9OLB.00	Attended diabetes structured education programme
26855	C108400	Unstable insulin dependant diabetes mellitus
28574	9h4..00	Exception reporting: diabetes quality indicators
28622	2126300	Diabetes resolved
28769	66AV.00	Diabetic on insulin and oral treatment
28856	8CP2.00	Transition of diabetes care options discussed
28873	66Ai.00	Diabetic 6 month review
29041	66AN.00	Date diabetic treatment start
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
30648	9N4p.00	Did not attend diabetic retinopathy clinic
31141	9OL8.00	Diabetes monitor.phone invite
31240	9OL7.00	Diabetes monitor.verbal invite
31241	9OLZ.00	Diabetes monitoring admin.NOS
31310	C108900	Insulin dependant diabetes maturity onset
32403	C107.11	Diabetes mellitus with gangrene
32556	C107.12	Diabetes with gangrene
32619	66Af.00	Patient diabetes education review
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
33254	C105.00	Diabetes mellitus with ophthalmic manifestation
33343	C10y.00	Diabetes mellitus with other specified manifestation
33807	C107200	Diabetes mellitus, adult with gangrene
34268	C10F200	Type 2 diabetes mellitus with neurological complications
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
34528	3882.00	Diabetes well being questionnaire
34541	8HVU.00	Private referral to diabetologist
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
35107	C104z00	Diabetes mellitis with nephropathy NOS
35288	C10E800	Type 1 diabetes mellitus - poor control
35383	9OLD.00	Diabetic patient unsuitable for digital retinal photography
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
36695	C10D.00	Diabetes mellitus autosomal dominant type 2

37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
38103	9N0m.00	Seen in diabetic nurse consultant clinic
38129	9N0o.00	Seen in community diabetic specialist nurse clinic
38130	ZRB6.00	Diabetes wellbeing questionnaire
38161	C108711	Type I diabetes mellitus with retinopathy
38617	C101y00	Other specified diabetes mellitus with ketoacidosis
38986	C100.00	Diabetes mellitus with no mention of complication
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
40682	C10E900	Type 1 diabetes mellitus maturity onset
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy
41049	C108712	Type 1 diabetes mellitus with retinopathy
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
41686	Cyu2000	[X]Other specified diabetes mellitus
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
42762	C109612	Type 2 diabetes mellitus with retinopathy
42831	C10E200	Type 1 diabetes mellitus with neurological complications
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
43227	C10F311	Type II diabetes mellitus with multiple complications
43453	C10C.00	Diabetes mellitus autosomal dominant
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
43857	C10M.00	Lipoatrophic diabetes mellitus
43921	C10E400	Unstable type 1 diabetes mellitus
43951	66AK.00	Diabetic - cooperative patient
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
44312	9M10.00	Informed dissent for diabetes national audit
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma

44443	C108500	Insulin dependent diabetes mellitus with ulcer
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
45276	C10E312	Insulin dependent diabetes mellitus with multiple complicat
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
45491	C10z.00	Diabetes mellitus with unspecified complication
45913	C109712	Type 2 diabetes mellitus - poor control
45914	C108812	Type 1 diabetes mellitus - poor control
45919	C109212	Type 2 diabetes mellitus with neurological complications
46150	C109512	Type 2 diabetes mellitus with gangrene
46290	C108y00	Other specified diabetes mellitus with multiple comps
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
46521	9N2d.00	Seen by diabetologist
46624	C10C.11	Maturity onset diabetes in youth
46850	C108811	Type I diabetes mellitus - poor control
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
46963	C108000	Insulin-dependent diabetes mellitus with renal complications
47011	8Hj0.00	Referral to diabetes structured education programme
47032	8CS0.00	Diabetes care plan agreed
47315	C10F711	Type II diabetes mellitus - poor control
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
47341	8A12.00	Diabetic crisis monitoring
47370	8HLE.00	Diabetology D.V. done
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
47409	C109B11	Type II diabetes mellitus with polyneuropathy
47582	C10E000	Type 1 diabetes mellitus with renal complications
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
47650	C10E300	Type 1 diabetes mellitus with multiple complications
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
47954	C10F900	Type 2 diabetes mellitus without complication
48192	C109E11	Type II diabetes mellitus with diabetic cataract
49074	C10F400	Type 2 diabetes mellitus with ulcer
49146	C108211	Type I diabetes mellitus with neurological complications
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
49655	C10F611	Type II diabetes mellitus with retinopathy
49869	C109G12	Type 2 diabetes mellitus with arthropathy

49884	6761.00	Diabetic pre-pregnancy counselling
49949	C10E411	Unstable type I diabetes mellitus
50175	66AW.00	Diabetic foot risk assessment
50225	C109011	Type II diabetes mellitus with renal complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
50972	C100z00	Diabetes mellitus NOS with no mention of complication
51261	C10E.12	Insulin dependent diabetes mellitus
51697	C10G.00	Secondary pancreatic diabetes mellitus
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
51957	C108511	Type I diabetes mellitus with ulcer
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn
52212	Cyu2.00	[X]Diabetes mellitus
52236	C10A.00	Malnutrition-related diabetes mellitus
52237	9360.00	Patient held diabetic record issued
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
53238	66AG.00	Diabetic drug side effects
53392	C10F911	Type II diabetes mellitus without complication
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath
54600	C10E412	Unstable insulin dependent diabetes mellitus
54601	9NN8.00	Under care of diabetologist
54846	9OL9.00	Diabetes monitoring deleted
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
55075	C109411	Type II diabetes mellitus with ulcer
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
56448	C108A00	Insulin-dependent diabetes without complication
56803	C107400	NIDDM with peripheral circulatory disorder
57278	C10F011	Type II diabetes mellitus with renal complications
57723	8HHy.00	Referral to diabetic register
58604	C109611	Type II diabetes mellitus with retinopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
59288	C103y00	Other specified diabetes mellitus with coma
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy

59725	C109111	Type II diabetes mellitus with ophthalmic complications
59903	C106.11	Diabetic amyotrophy
59991	C10D.11	Maturity onset diabetes in youth type 2
60107	C108411	Unstable type I diabetes mellitus
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy
60499	C108600	Insulin dependent diabetes mellitus with gangrene
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
61021	68AB.00	Diabetic digital retinopathy screening offered
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
61344	C108011	Type I diabetes mellitus with renal complications
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
61523	C106y00	Other specified diabetes mellitus with neurological comps
61557	8HKE.00	Diabetology D.V. requested
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
61829	C108212	Type 1 diabetes mellitus with neurological complications
62107	C109511	Type II diabetes mellitus with gangrene
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
62352	C108H11	Type I diabetes mellitus with arthropathy
62613	C10EA11	Type I diabetes mellitus without complication
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
63017	C108911	Type I diabetes mellitus maturity onset
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
63412	8CR2.00	Diabetes clinical management plan
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
64142	8Hl1.00	Referral for diabetic retinopathy screening
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
64357	C10zz00	Diabetes mellitus NOS with unspecified complication
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy
64449	C108z00	Unspecified diabetes mellitus with multiple complications
64571	C109C11	Type II diabetes mellitus with nephropathy
64668	C10FJ11	Insulin treated Type II diabetes mellitus
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder

65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
65267	C10F300	Type 2 diabetes mellitus with multiple complications
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
65704	C109412	Type 2 diabetes mellitus with ulcer
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
66274	66Ah.00	Insulin needles changed for each injection
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
66675	C10A000	Malnutrition-related diabetes mellitus with coma
66872	C108D11	Type I diabetes mellitus with nephropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
67212	C10H000	DM induced by non-steroid drugs without complication
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
67905	C109211	Type II diabetes mellitus with neurological complications
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
68390	C108512	Type 1 diabetes mellitus with ulcer
68546	ZRB4.00	Diabetes clinic satisfaction questionnaire
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
69124	C107300	IDDM with peripheral circulatory disorder
69152	66Aj.00	Insulin needles changed less than once a day
69163	8HTi.00	Referral to multidisciplinary diabetic clinic
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
69676	C10EA00	Type 1 diabetes mellitus without complication
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
69993	C10E600	Type 1 diabetes mellitus with gangrene
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
72333	8HME.00	Listed for Diabetology admissn
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
72702	C10E812	Insulin dependent diabetes mellitus - poor control
82474	8Hl4.00	Referral to community diabetes specialist nurse
83485	66Am.00	Insulin dose changed
83532	66Ao.00	Diabetes type 2 review
85660	66An.00	Diabetes type 1 review

85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
90301	66Ag.00	Insulin needles changed daily
91646	C10F411	Type II diabetes mellitus with ulcer
91942	C10E311	Type I diabetes mellitus with multiple complications
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
93390	9OLH.00	Attended DAFNE diabetes structured education programme
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
93491	9OLJ.00	DAFNE diabetes structured education programme completed
93529	9OLK.00	DESMOND diabetes structured education programme completed
93530	9OLE.00	Attended DESMOND structured programme
93631	9OLL.00	XPERT diabetes structured education programme completed
93657	8Hj4.00	Referral to DESMOND diabetes structured education programme
93704	8Hj3.00	Referral to DAFNE diabetes structured education programme
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
93854	9OLM.00	Diabetes structured education programme declined
93870	8Hj5.00	Referral to XPERT diabetes structured education programme
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
93878	C10E511	Type I diabetes mellitus with ulcer
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
94011	9OLG.00	Attended XPERT diabetes structured education programme
94186	9OLF.00	Diabetes structured education programme completed
94330	8H4e.00	Referral to diabetes special interest general practitioner
94383	C10N000	Secondary diabetes mellitus without complication
94699	ZRB5.00	Diabetes treatment satisfaction questionnaire
94955	9NiE.00	Did not attend XPERT diabetes structured education programme
94956	8I84.00	Did not complete XPERT diabetes structured education program
95093	8I83.00	Did not complete DESMOND diabetes structured educat program
95094	8I81.00	Did not complete diabetes structured education programme
95159	9NiD.00	Did not attend DESMOND diabetes structured education program
95343	C10E711	Type I diabetes mellitus with retinopathy
95539	C10FS00	Maternally inherited diabetes mellitus
95553	9NiA.00	Did not attend diabetes structured education

		programme
95636	C10ER00	Latent autoimmune diabetes mellitus in adult
95813	9N1o.00	Seen in multidisciplinary diabetic clinic
95992	C108A11	Type I diabetes mellitus without complication
95994	66Aq.00	Diabetic foot screen
96010	66Ap.00	Insulin treatment initiated
96235	C10E911	Type I diabetes mellitus maturity onset
96506	C10G000	Secondary pancreatic diabetes mellitus without complication
97281	9Nl4.00	Seen by general practitioner special interest in diabetes
97446	C108912	Type 1 diabetes mellitus maturity onset
97474	C108412	Unstable type 1 diabetes mellitus
97809	8I82.00	Did not complete DAFNE diabetes structured education program
97849	C10E912	Insulin dependent diabetes maturity onset
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
98392	C10C.12	Maturity onset diabetes in youth type 1
98616	C10F211	Type II diabetes mellitus with neurological complications
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
98954	3883.00	Diabetes treatment satisfaction questionnaire
99231	C108B11	Type I diabetes mellitus with mononeuropathy
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
99719	C10EA12	Insulin-dependent diabetes without complication
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn

Codes used to identify all cardiovascular events

CPRD Medcode	Read code	Read term
240	G3...00	Ischaemic heart disease
1344	G340.12	Coronary artery disease
1490	G5z..00	Heart disease NOS
1628	3213100	Exercise ECG abnormal
1655	G340.11	Triple vessel disease of the heart
1676	G3z..00	Ischaemic heart disease NOS
1792	G3...13	IHD - Ischaemic heart disease
1811	G5yz.00	Other heart disease NOS
2491	G30..12	Coronary thrombosis
3997	1J6..00	Suspected heart disease
3999	G340000	Single coronary vessel disease
5254	G340100	Double coronary vessel disease
5413	G340.00	Coronary atherosclerosis
7320	G343.00	Ischaemic cardiomyopathy
8246	322..00	ECG: myocardial ischaemia
8568	G37..00	Cardiac syndrome X
9276	G31y000	Acute coronary insufficiency
9413	G31y.00	Other acute and subacute ischaemic heart disease
13571	G30..16	Thrombosis - coronary
15661	G310.11	Dressler's syndrome
15754	G34z.00	Other chronic ischaemic heart disease NOS
17133	G30A.00	Mural thrombosis
18134	182A.00	Chest pain on exertion
18889	G34z000	Asymptomatic coronary heart disease
20416	G3...12	Atherosclerotic heart disease
21844	G31y300	Transient myocardial ischaemia
22383	G3y..00	Other specified ischaemic heart disease
23078	G34y100	Chronic myocardial ischaemia
24540	G34y000	Chronic coronary insufficiency
24683	G5y1.00	Myocardial degeneration
24783	G3...11	Arteriosclerotic heart disease
26965	32F2.00	ECG: T wave abnormal
26966	32E3.00	ECG: S-T elevation
26967	32F4.00	ECG: T wave inverted
26973	3222	ECG:shows myocardial ischaemia
27951	G31..00	Other acute and subacute ischaemic heart disease
27977	G31yz00	Other acute and subacute ischaemic heart disease NOS
28138	G34..00	Other chronic ischaemic heart disease
29421	G344.00	Silent myocardial ischaemia
30171	G5...00	Other forms of heart disease
32450	G33z400	Ischaemic chest pain

34633	G34y.00	Other specified chronic ischaemic heart disease
35287	322Z.00	ECG: myocardial ischaemia NOS
35713	G34yz00	Other specified chronic ischaemic heart disease NOS
36193	G5y..00	Other specified heart disease
36523	G311.00	Preinfarction syndrome
36609	G342.00	Atherosclerotic cardiovascular disease
39449	G312.00	Coronary thrombosis not resulting in myocardial infarction
39655	G311.12	Impending infarction
39693	G31y200	Subendocardial ischaemia
41179	G5yyz00	Other ill-defined heart disease NOS
42104	32E4.00	ECG: S-T depression
47637	Gyu3300	[X]Other forms of chronic ischaemic heart disease
52517	Gyu3.00	[X]Ischaemic heart diseases
54251	G311z00	Preinfarction syndrome NOS
56621	G5y2.00	Cardiovascular arteriosclerosis unspecified
57334	G557300	Gouty tophi of heart
59687	G5yy.00	Other ill-defined heart disease
68401	Gyu3200	[X]Other forms of acute ischaemic heart disease
95550	8H2V.00	Admit ischaemic heart disease emergency

Codes used to identify angina

CPRD Medcode	Read code	Read term
1414	G33z300	Angina on effort
1430	G33..00	Angina pectoris
1431	G311.13	Unstable angina
4656	G311.11	Crescendo angina
7347	G311100	Unstable angina
7696	G33z200	Syncope anginosa
9555	G33z500	Post infarct angina
11048	G331.11	Variant angina pectoris
11983	G311500	Acute coronary syndrome
12804	G33z700	Stable angina
12986	G331.00	Prinzmetal's angina
17307	G311200	Angina at rest
18118	G311400	Worsening angina
18125	G330000	Nocturnal angina
19655	G311.14	Angina at rest
19827	3213111	Positive exercise ECG test
20095	G330.00	Angina decubitus
25842	G33z.00	Angina pectoris NOS
26863	G33z600	New onset angina
28554	G33zz00	Angina pectoris NOS
29902	G330z00	Angina decubitus NOS
34328	G311300	Refractory angina
36854	G332.00	Coronary artery spasm
39546	Gyu3000	[X]Other forms of angina pectoris
54535	G33z100	Stenocardia
66388	G33z000	Status anginosus

Codes used to identify myocardial infarction

CPRD Medcode	Read code	Read term
241	G30..00	Acute myocardial infarction
1204	G30..14	Heart attack
1677	G30..15	MI - acute myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS
3704	G307.00	Acute subendocardial infarction
5387	G301.00	Other specified anterior myocardial infarction
7783	323..00	ECG: myocardial infarction
8935	G302.00	Acute inferolateral infarction
9507	G307000	Acute non-Q wave infarction
10562	G307100	Acute non-ST segment elevation myocardial infarction
12139	G300.00	Acute anterolateral infarction
12229	G30X000	Acute ST segment elevation myocardial infarction
13566	G30..11	Attack - heart
14658	G30z.00	Acute myocardial infarction NOS
14897	G301z00	Anterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
17689	G30..17	Silent myocardial infarction
17872	G301100	Acute anteroseptal infarction
18842	G35..00	Subsequent myocardial infarction
23579	G310.00	Postmyocardial infarction syndrome
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
23892	G304.00	Posterior myocardial infarction NOS
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
26972	3234	ECG:posterior/inferior infarct
26975	3233	ECG: antero-septal infarct.
28736	G30y000	Acute atrial infarction
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
29643	G303.00	Acute inferoposterior infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecif site
30330	G309.00	Acute Q-wave infarct
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
32272	G38..00	Postoperative myocardial infarction
32854	G30B.00	Acute posterolateral myocardial infarction
34803	G30y.00	Other acute myocardial infarction
36423	G36..00	Certain current complication follow acute myocardial infarct
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn

38609	G351.00	Subsequent myocardial infarction of inferior wall
40429	G301000	Acute anteroapical infarction
40996	7929111	Percut translum coronary thrombolytic therapy-streptokinase
41221	G30y200	Acute septal infarction
41835	G384.00	Postoperative subendocardial myocardial infarction
45809	G350.00	Subsequent myocardial infarction of anterior wall
46017	G30yz00	Other acute myocardial infarction NOS
46112	G380.00	Postoperative transmural myocardial infarction anterior wall
46166	G35X.00	Subsequent myocardial infarction of unspecified site
46276	G381.00	Postoperative transmural myocardial infarction inferior wall
52705	3236	ECG: lateral infarction
55401	3235	ECG: subendocardial infarct
59032	323Z.00	ECG: myocardial infarct NOS
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
62626	G30y100	Acute papillary muscle infarction
63467	G306.00	True posterior myocardial infarction
68357	G31y100	Microinfarction of heart
68748	G38z.00	Postoperative myocardial infarction, unspecified
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
72562	G353.00	Subsequent myocardial infarction of other sites
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
97001	44p2.00	Cardiac troponin positive
99991	Gyu3600	[X]Subsequent myocardial infarction of unspecified site

Codes used to identify all cerebrovascular disease

CPRD Medcode	Read code	Read term
1786	G60..00	Subarachnoid haemorrhage
2156	G631.11	Stenosis, carotid artery
2417	G65..13	Vertebro-basilar insufficiency
2418	G6...00	Cerebrovascular disease
2652	G634.00	Carotid artery stenosis
3535	G61z.00	Intracerebral haemorrhage NOS
3979	G672.00	Hypertensive encephalopathy
4152	G631.12	Thrombosis, carotid artery
4240	G631.00	Carotid artery occlusion
4273	G621.00	Subdural haemorrhage - nontraumatic
5051	G61..00	Intracerebral haemorrhage
5184	G670.11	Precerebral atherosclerosis
5185	G64z111	Lateral medullary syndrome
5268	G650.11	Insufficiency - basilar artery
7912	G614.00	Pontine haemorrhage
8837	G64..00	Cerebral arterial occlusion
9696	G604.00	Subarachnoid haemorrhage from posterior communicating artery
9843	G755000	Cranial arteritis
10062	G6z..00	Cerebrovascular disease NOS
10189	G674000	Cerebral amyloid angiopathy
10794	G656.00	Vertebrobasilar insufficiency
11171	G670.00	Cerebral atherosclerosis
12555	G671z00	Generalised ischaemic cerebrovascular disease NOS
12634	G673200	Carotid artery dissection
13564	G613.00	Cerebellar haemorrhage
13577	G67..00	Other cerebrovascular disease
15019	G641.00	Cerebral embolism
16507	G65z100	Intermittent cerebral ischaemia
16517	G640.00	Cerebral thrombosis
17326	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
17734	G622.00	Subdural haematoma - nontraumatic
18689	G660.00	Middle cerebral artery syndrome
18912	G623.00	Subdural haemorrhage NOS
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
19260	G662.00	Posterior cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19412	G602.00	Subarachnoid haemorrhage from middle cerebral artery
20284	G62z.00	Intracranial haemorrhage NOS
21118	G651000	Vertebro-basilar artery syndrome
22018	G673000	Dissection of cerebral arteries, nonruptured

22400	G674.00	Cerebral arteritis
22677	G70y011	Carotid artery disease
23361	G68..00	Late effects of cerebrovascular disease
23465	G652.00	Subclavian steal syndrome
23580	G60z.00	Subarachnoid haemorrhage NOS
23942	G650.00	Basilar artery syndrome
24385	G671100	Chronic cerebral ischaemia
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
29939	G600.00	Ruptured berry aneurysm
30045	G616.00	External capsule haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
31595	G610.00	Cortical haemorrhage
31704	G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
31805	G62..00	Other and unspecified intracranial haemorrhage
31876	G72y000	Aneurysm of common carotid art
32447	G630.00	Basilar artery occlusion
33377	G651.00	Vertebral artery syndrome
33499	G665.00	Pure motor lacunar syndrome
34117	G67y.00	Other cerebrovascular disease OS
34758	G641.11	Cerebral embolus
35059	G673100	Carotico-cavernous sinus fistula
36178	G620.00	Extradural haemorrhage - nontraumatic
36390	G72y200	Aneurysm of internal carotid artery
37199	G70y000	Carotid artery atherosclerosis
37493	G67z.00	Other cerebrovascular disease NOS
37947	G676.00	Nonpyogenic venous sinus thrombosis
40053	G671.00	Generalised ischaemic cerebrovascular disease NOS
40338	G611.00	Internal capsule haemorrhage
40847	G632.00	Vertebral artery occlusion
41910	G605.00	Subarachnoid haemorrhage from basilar artery
42331	G603.00	Subarachnoid haemorrhage from anterior communicating artery
43451	G682.00	Sequelae of other nontraumatic intracranial haemorrhage
44740	G680.00	Sequelae of subarachnoid haemorrhage
44765	G653.00	Carotid artery syndrome hemispheric
45781	G63..00	Precerebral arterial occlusion
46316	G612.00	Basal nucleus haemorrhage
47642	G64z100	Wallenberg syndrome
48149	G681.00	Sequelae of intracerebral haemorrhage
50594	G654.00	Multiple and bilateral precerebral artery syndromes
50678	G72y100	Aneurysm of external carotid artery
51138	G68W.00	Sequelae/other + unspecified cerebrovascular diseases

51311	G6y..00	Other specified cerebrovascular disease
51326	G63y.00	Other precerebral artery occlusion
51759	G677000	Occlusion and stenosis of middle cerebral artery
51767	G666.00	Pure sensory lacunar syndrome
54744	F11x200	Cerebral degeneration due to cerebrovascular disease
55247	G65z000	Impending cerebral ischaemia
55602	G677300	Occlusion and stenosis of cerebellar arteries
56007	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
57315	G618.00	Intracerebral haemorrhage, multiple localized
57527	G677100	Occlusion and stenosis of anterior cerebral artery
60692	G606.00	Subarachnoid haemorrhage from vertebral artery
62342	G615.00	Bulbar haemorrhage
63830	G63..12	Stenosis of precerebral arteries
65770	G677200	Occlusion and stenosis of posterior cerebral artery
70536	G671000	Acute cerebrovascular insufficiency NOS
71274	G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
71585	G63z.00	Precerebral artery occlusion NOS
73901	Gyu6.00	[X]Cerebrovascular diseases
90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
97122	G673300	Vertebral artery dissection
98188	G679.00	Small vessel cerebrovascular disease
98642	G633.00	Multiple and bilateral precerebral arterial occlusion
99367	Gyu6A00	[X]Other cerebrovascular disorders in diseases CE

Codes used to identify cerebrovascular accident (stroke)

CPRD Medcode	Read code	Read term
569	G64..12	Infarction - cerebral
1298	G66..11	CVA unspecified
1469	G66..00	Stroke and cerebrovascular accident unspecified
3149	G64z.00	Cerebral infarction NOS
5363	G64..11	CVA - cerebral artery occlusion
5602	G64z.12	Cerebellar infarction
6116	G66..13	CVA - Cerebrovascular accident unspecified
6155	G64..13	Stroke due to cerebral arterial occlusion
6228	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
6253	G66..12	Stroke unspecified
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
7780	G667.00	Left sided CVA
8443	G663.00	Brain stem stroke syndrome
9985	G64z200	Left sided cerebral infarction
10504	G64z300	Right sided cerebral infarction
12833	G668.00	Right sided CVA
15252	G64z.11	Brainstem infarction NOS
16956	G669.00	Cerebral palsy, not congenital or infantile, acute
17322	G664.00	Cerebellar stroke syndrome
18604	G61..12	Stroke due to intracerebral haemorrhage
23671	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
24446	G63y100	Cerebral infarction due to embolism of precerebral arteries
25615	G64z000	Brainstem infarction
26424	G64z400	Infarction of basal ganglia
27975	G641000	Cerebral infarction due to embolism of cerebral arteries
33543	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
39344	G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
39403	G683.00	Sequelae of cerebral infarction
40758	G6W..00	Cereb infarct due unsp occlus/stenos precerebr artrs
53745	Gyu6400	[X]Other cerebral infarction
57495	G63..11	Infarction - precerebral
91627	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
94482	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries

Codes used to identify transient ischaemic attack

CPRD Medcode	Read code	Read term
504	G65..00	Transient cerebral ischaemia
1433	G65..12	Transient ischaemic attack
1895	G65z.00	Transient cerebral ischaemia NOS
6489	G655.00	Transient global amnesia
15788	G65zz00	Transient cerebral ischaemia NOS
19354	G65y.00	Other transient cerebral ischaemia

Codes used to identify peripheral vascular disease

CPRD Medcode	Read code	Read term
1517	G73z000	Intermittent claudication
1826	G73..12	Ischaemia of legs
2760	G73zz00	Peripheral vascular disease NOS
3530	G73z.00	Peripheral vascular disease NOS
4325	G73yz00	Other specified peripheral vascular disease NOS
5414	G732000	Gangrene of toe
5702	G73..11	Peripheral ischaemic vascular disease
5943	G73..00	Other peripheral vascular disease
6827	G73..13	Peripheral ischaemia
9099	7A47.00	Other emergency bypass of femoral artery or popliteal artery
9204	G732.00	Peripheral gangrene
11766	7A47.16	Other emergency bypass of femoral artery
12735	G732100	Gangrene of foot
14797	G702.00	Extremity artery atheroma
16148	SP12.00	Peripheral vascular complications of care
16260	G702z00	Extremity artery atheroma NOS
16284	G701.00	Renal artery atherosclerosis
23871	G73y100	Peripheral angiopathic disease EC NOS
38907	G73y.00	Other specified peripheral vascular disease
43648	7A41211	Emergency femoro-femoral prosthetic cross over graft
43651	7A47000	Emerg bypass femoral art by fem/pop art anast c prosth NEC
44250	7A41000	Emerg bypass iliac art by iliac/femoral art anastomosis NEC
48939	7A47C00	Emerg bypass femoral artery by fem/fem art anastomosis NEC
52342	7A47200	Emerg bypass femoral art by fem/pop a anast c vein graft NEC
60693	7A47300	Emerg bypass pop art by pop/pop art anast c vein graft NEC
62775	7A47B00	Emerg bypass pop art by pop/peron art anast c vein graft NEC
63238	7A47.13	Other emergency bypass of deep femoral artery
65692	7A47y00	Other emergency bypass of femoral or popliteal artery OS
66820	7A47400	Emerg bypass femoral art by fem/tib art anast c prosth NEC
66879	7A47700	Emerg bypass pop art by pop/tib art anast c vein graft NEC
66917	7A41600	Emerg bypass leg artery by aorta/com fem art anastomosis NEC
67818	7A47100	Emerg bypass popliteal art by pop/pop art anast c

		prosth NEC
68141	7A41400	Emerg bypass comm iliac art by aorta/com iliac art anast NEC
68320	7A47z00	Other emergency bypass of femoral or popliteal artery NOS
70922	7A47D00	Emerg bypass popliteal artery by pop/fem art anastomosis NEC
72448	7A41200	Emerg bypass iliac artery by femoral/femoral art anast NEC
72491	7A47.11	Other emerg bypass femoral or popliteal art by anastomosis
73961	Gyu7400	[X]Other specified peripheral vascular diseases
96255	7A47600	Emerg bypass femoral art by fem/tib a anast c vein graft NEC
97606	7A47.15	Other emergency bypass of superficial femoral artery
98174	G733.00	Ischaemic foot
99676	7A47800	Emerg bypass femoral art by fem/peron art anast c prosth NEC
100113	7A47.12	Other emergency bypass of common femoral artery

Appendix 3 – Peer-reviewed publications

European Journal of Preventive Cardiology

Original scientific paper

European Journal of Preventive Cardiology
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Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis

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Abstract

Background: Hyperuricaemia, the biochemical precursor to gout, has been shown to be an independent risk factor for mortality from cardiovascular disease (CVD), although studies examining the clinical phenomenon of gout and risk of CVD mortality report conflicting results. This study aimed to produce a pooled estimate of risk of mortality from cardiovascular disease in patients with gout.

Design: Systematic review and meta-analysis.

Methods: Electronic bibliographic databases were searched from inception to November 2012, with results reviewed by two independent reviewers. Studies were included if they reported data on CVD mortality in adults with gout who were free of CVD at time of entry into the study. Pooled hazard ratios (HRs) for this association were calculated both unadjusted and adjusted for traditional vascular risk factors.

Results: Six papers, including 223,448 patients, were eligible for inclusion (all (CVD) mortality $n = 4$, coronary heart disease (CHD) mortality $n = 3$, and myocardial infarction mortality $n = 3$). Gout was associated with an excess risk of CVD mortality (unadjusted HR 1.51 (95% confidence interval, CI, 1.17–1.84)) and CHD mortality (unadjusted HR 1.59, 95% CI 1.25–1.94)). After adjusting for traditional vascular risk factors, the pooled HR for both CVD mortality (HR 1.29, 95% CI 1.14–1.44) and CHD mortality (HR 1.42, 95% CI 1.22–1.63) remained statistically significant, but none of the studies reported a significant association with myocardial infarction.

Conclusions: Gout increases the risk of mortality from CVD and CHD, but not myocardial infarction, independently of vascular risk factors.

Keywords
Cardiovascular disease, coronary heart disease, gout, mortality, myocardial infarction

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Introduction

Gout is the most common form of inflammatory arthritis and is estimated to affect 1.4% of the population in the UK and Germany and 4% in the USA.[1,2] In recent literature, both hyperuricaemia (the biochemical precursor to gout) and other inflammatory arthritides have been shown to be independent risk factors for mortality from cardiovascular disease (CVD).[3–6] Several mechanisms for these associations have been suggested, including immobility resulting from joint pain and the additional cardiovascular risk conferred by medications (such as nonsteroidal anti-inflammatory drugs) used to manage these conditions.[7] Latterly, it has been suggested that systemic inflammation leads to atherogenesis via endothelial dysfunction, decreased arterial compliance, impaired blood flow, and thus a proatherogenic state.[8] Therefore patients with gout may be at increased vascular risk due to both hyperuricaemia and crystal-induced inflammation,

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now recognized to persist even in the asymptomatic intercritical period.[9]

However, the precise nature of the relationship remains unclear since gout and CVD share many common risk factors, such as hypertension and obesity,[10] introducing a potential source of confounding.

Epidemiological studies examining the relationship between gout and mortality from CVD have, to date, reported conflicting findings even where they are undertaken in similar populations and geographical areas.[11,12] Although one systematic review has been published, no attempt was made to pool the data described.[13]

For this reason, a systematic review and meta-analysis was undertaken to pool estimates of risk from existing studies in order to examine the relationship between gout and mortality from CVD.

Methods

Data sources and searches

Four electronic databases (MEDLINE, EMBASE, CINAHL, and The Cochrane Library) were searched from their inception until 17 November 2012, for studies of the association between gout and cardiovascular mortality. Search terms describing gout (both free-text and using database specific indexing trees) were combined using the Boolean operator 'AND' with terms describing the outcome of cardiovascular mortality. A full list of search terms is available as an online supplement. Reference lists of relevant reports and review articles were screened to identify additional sources of data.

Study selection

Studies were eligible for inclusion if they were of a trial or epidemiological design (cohort, cross-sectional), included adults aged 18 and over, and examined the association of interest in a cohort of patients free from vascular disease at diagnosis of gout. Case–control studies were not included due to the likelihood of sampling and recall bias associated with this design. No geographical or language restrictions were imposed.

Two authors (LC, PC) independently screened all of the titles and abstracts, after which, for those considered potentially relevant, full-text articles were independently reviewed to determine eligibility for inclusion. A third reviewer (SH) was identified in case of disagreement or uncertainty. Studies reporting different definitions of cardiovascular mortality were grouped according to these definitions for analysis. All studies reported mortality coded according to the International Classification of Disease 9th or 10th revision, with comparisons suggesting both revisions identify a similar prevalence of medical conditions.[14] Studies were included if they reported mortality from any of: any CVD (ICD-9 codes 390–459, ICD-10 codes I00–I99), coronary heart disease (CHD: including myocardial infarction, MI; ICD-9 codes 410–414, ICD-10 codes I20–I25), or specifically MI (ICD-9 code 414, ICD-10 codes I21–I22).

Data extraction and quality assessment

Data extraction and quality assessment was undertaken by two reviewers independently (LC, PC), using a specifically designed data extraction form. Methodological quality assessment criteria were based upon the Newcastle–Ottawa scale.[15] This consists of three components; selection of study group, quality of adjustment for confounding, and ascertainment of the outcome of interest in the cohorts (maximum score of nine). Two additional outcome criteria were added, assessing the appropriateness of statistical methods and the separation of patients with gout from those with asymptomatic hyperuricaemia. Authors were contacted for additional information where necessary. Higher methodological quality is indicated by a higher score.

Data synthesis and analysis

Pooled estimates of hazard ratios (HRs) were calculated using the DerSimonian and Laird random-effects model,[16] for mortality from any CVD or CHD. This technique weights individual studies according to sample size and variance, giving a pooled estimate and 95% confidence interval. A random effects model was chosen due to the number of papers included and the likelihood of heterogeneity across study populations. I^2 was used to calculate heterogeneity between studies, estimating the percentage of variability in results attributed to between-study differences.[17] Statistical analysis was performed using STATA IC 12. Publication bias was assessed using funnel plots. Begg's rank correlation test and Egger's linear regression test were used to detect any asymmetry in the funnel plot that may be due to publication bias.[18,19]

Results

Description of the studies

The initial search identified 1293 potentially relevant papers. After title and abstract screening, 1192 papers were excluded either because they did not examine the association of interest or were editorial or discursive articles. The remaining 101 papers were reviewed in

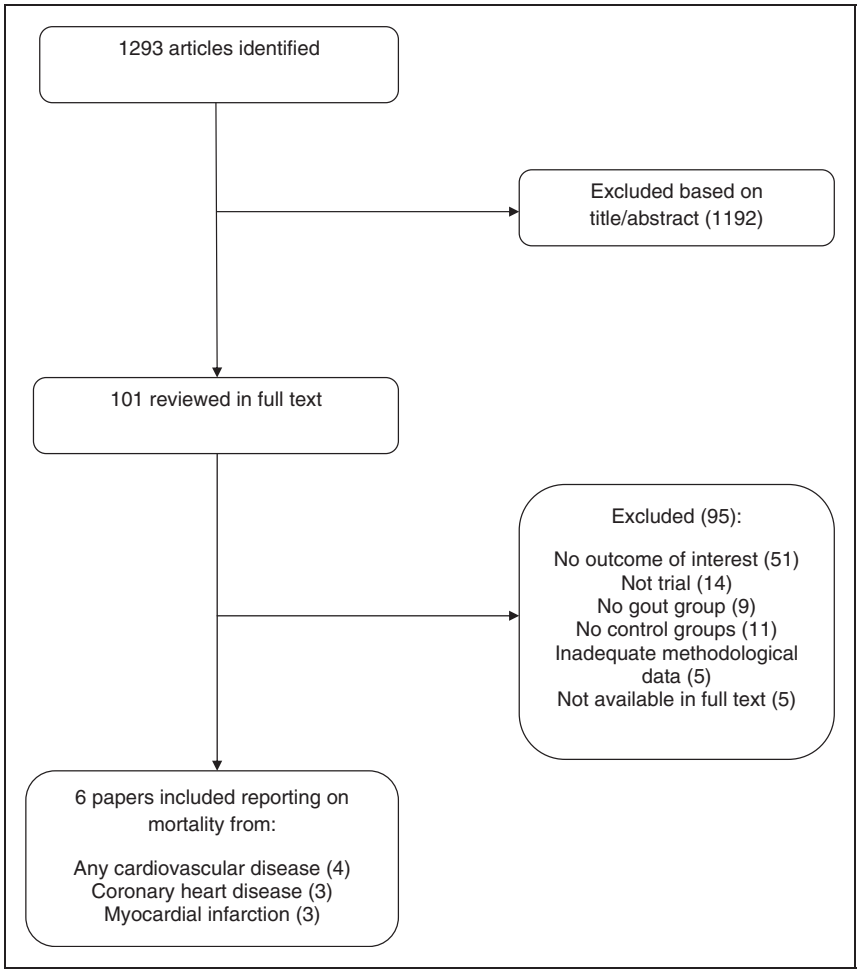

Figure 1. Selection of studies included in the review.

full text, and of these 95 were excluded (Figure 1). Six studies reporting outcomes for 223,448 patients were included: 149,532 men and 73,916 women. Four studies reported on mortality from any CVD,[11,12,20,21] three reported on mortality from CHD,[11,12,20] and three reported on mortality from MI.[11,22,23] Two studies were conducted in Asia[20,21] and four in the USA or Canada.[11,12,22,23] Numbers of participants ranged from 9105[12] to 57,852.[23] Three studies included male-only study populations.[11,12,22] Follow up ranged from 56 months[20] to 17 years.[12] The characteristics of the included studies are described in Table 1.

Scores for methodological quality of studies, where the maximum score was 11, ranged from nine[11,12] to 11,[21] indicating a high level of methodological quality in all included studies.

Gout and mortality from any CVD

The pooled estimate of unadjusted HR for mortality due to any CVD based on four studies was 1.51 (95% CI 1.17–1.84) (comparing patients with gout to those without gout).[11,12,20,21] A significant degree of study heterogeneity was noted ($I^2 = 66.8\%$, $p = 0.029$). Based on the same four studies, after adjustment for vascular risk factors, the pooled multivariate HR for mortality due to any CVD was 1.29 (95% CI 1.13–1.44), with no statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.541$) (Figure 2). The individual vascular risk factors adjusted for in each study are shown in Table 1. Examining the effect of gender on overall CVD mortality, two studies included only men,[11,12] and whilst one study included both men and women, so a separate analysis by gender was not undertaken.[20] One study reported risk of CVD mortality by gender, but did not find increased risk in either gender (men: HR 1.10, 95% CI 0.82–1.46; women: HR 1.51, 95% CI 1.00–2.30).[21]

Gout and mortality from CHD

The pooled estimate of unadjusted HR for mortality due to CHD based on three studies was 1.59 (95% CI 1.25–1.94) (comparing patients with gout to those

Table 1. Characteristics of included studies

Publication	No. of participants (% male)	Age, years (mean + SD)	Follow up (years)	Gout definition	Outcome definition (no. of deaths)	Covariates in multivariable analysis
Krishnan et al.[22]	12,866 (100)	Overall: 46 ± 6 Gout: 47 ± 5 Not gout: 46 ± 6	6.5	Self report of physician diagnosis + documented sustained hyperuricaemia	Fatal acute MI (246)	Clustering within arms of the study, age, blood pressure, serum cholesterol level, serum creatinine level, diabetes, smoking, family history of MI, aspirin use, diuretic use, alcohol use, BMI, serum uric acid level
Choi and Curhan[11]	47,258 (100)	Gout: 59 Not gout: 54 (SD not reported)	12	Self report of physician diagnosis	All cardiovascular deaths (2132) Fatal CHD (1576)	Age, hypertension, hypercholesterolaemia, aspirin/diuretic use, diabetes, smoking, BMI, physical activity, alcohol, family history of MI, energy intake, trans fat, dietary cholesterol, protein, linoleic fatty acid, ratio of polyunsaturated to unsaturated fat
Krishnan et al.[12]	9105 (100)	Gout: 52.9 ± 5.8 Not gout: 52.1 ± 5.9	17	Self report or physician diagnosis + documented sustained hyperuricaemia OR use of gout medication in the preceding 5y OR self report of gout without urate level	Death from any cardiovascular end-point (1241) Fatal MI (360) Fatal CHD (833)	Age, systolic and diastolic blood pressure, low-density lipoprotein cholesterol levels, high-density lipoprotein cholesterol levels, plasma triglyceride levels, serum creatinine levels, fasting glucose level, cigarettes per day, family history of MI, aspirin use, diuretic use, alcoholic drinks per day, BMI
DeVera et al.[23]	57,852 (59.7)	Gout M: 73.9 ± 6.4 F: 75 ± 6.8 Not gout M: 73.3 ± 6.4 F: 75.0 ± 6.8	7	ICD-9 coded	Fatal acute MI (778)	Age, hypertension, diabetes, COPD, hyperlipidaemia, Charlson comorbidity score, monthly prescription drug use of NSAIDs, aspirin, glucocorticoids, statins, anticoagulants, HRT, diuretics

(continued)

Table 1. Continued

Publication	No. of participants (% male)	Age, years (mean + SD)	Follow up (years)	Gout definition	Outcome definition (no. of deaths)	Covariates in multivariable analysis
Kuo et al.[20]	49,332 (53.4)	Gout: 52 ± 11 Not gout: 50 ± 11	4.7	Physican recorded (either crystals present in joint aspirate or ICD-9 gout code) OR self report	Cardiovascular mortality (198)	Normouricaemia/hyperuricaemia/gout, age, gender, number of components of metabolic syndrome, proteinuria
Teng et al.[21]	47,035 (41.4)	Gout: 61.5 ± 7.7 Not gout: 61.6 ± 8.0	8.1	Self report of physician diagnosis + self report of elevated serum urate + self report of dietary advice for gout	All cardiovascular deaths (1526) CHD deaths (855)	Age at follow up, years between baseline and follow up, BMI, gender, dialect group, education, alcohol consumption, physical activity, cigarette smoking, dietary saturated fat density, dietary cholesterol density, hypertension, diabetes

BMI, body mass index; MI, myocardial infarction; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; HRT, hormone-replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.

without gout).[11,12,21] Moderate heterogeneity was noted ($I^2 = 55\%$, $p = 0.108$). Based on the same three studies, after adjustment for vascular risk factors, the pooled multivariate HR for mortality due to CHD was 1.42 (95% CI 1.22–1.63), with no statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.660$) (Figure 3). Two of these studies used a solely male population.[11,12] In the remaining study, an increased risk of mortality from CHD was reported in women, HR 1.81, 95% CI 1.07–3.05), but not men, HR 1.16, 95% CI 0.81–1.67).[21]

Gout and mortality from MI

Three studies report on the association between gout and mortality from MI. However, these studies were unsuitable for meta-analysis due to significant heterogeneity in the statistical analysis undertaken and outcomes reported, and thus are described.

One study, from the USA, reported no increased risk of fatal MI in 1123 men with gout compared to 11,743 age-matched male controls (odds ratio, OR, 0.96, 95% CI 0.66–1.44).[22] However, another paper reporting results from this same study using a smaller population of 655 men with gout compared to 8450 without did report an excess risk of mortality from MI in gout patients (HR 1.46, 95% CI 1.03–2.06).[12] A further study from Canada reported an excess risk of mortality from MI in a mixed population of 9642 gout patients compared to 48210 controls, but reported an increased mortality risk only for women with gout ($n = 3890$) (HR 1.57, 95% CI 1.18–2.09), but not men (HR 1.19, 95% CI 0.96–1.49).[23] After adjustment for vascular risk factors, none of the studies report a statistically significant excess risk of mortality from MI in gout patients of either gender.

Publication bias assessment

No evidence of publication bias was seen for either any CVD mortality (Begg's tests: crude $p = 0.149$, multivariate $p = 0.734$; Egger's tests: crude $p = 0.06$, multivariate $p = 0.442$) or CHD mortality (Begg's tests: crude $p = 0.296$, multivariate $p = 0.296$; Egger's tests: crude $p = 0.164$, multivariate $p = 0.197$).

Discussion

This systematic review and meta-analysis found a significant association between gout and mortality from any CVD and CHD. It does not support an association between gout and mortality from MI based upon current evidence.

Our results are consistent with a previous systematic review of four studies,[13] which concluded that gout is an independent risk factor for cardiovascular mortality.

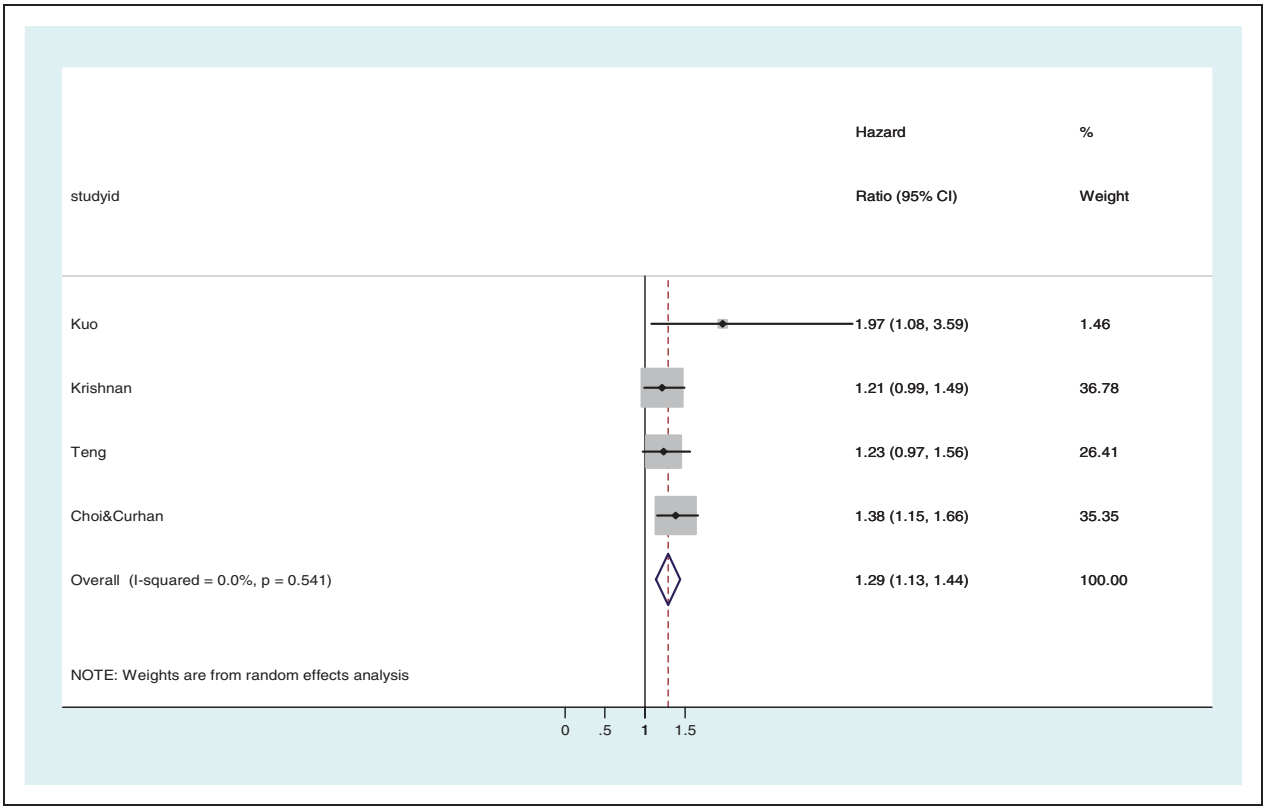

Figure 2. Meta-analysis of adjusted findings of studies reporting mortality from any cardiovascular disease.

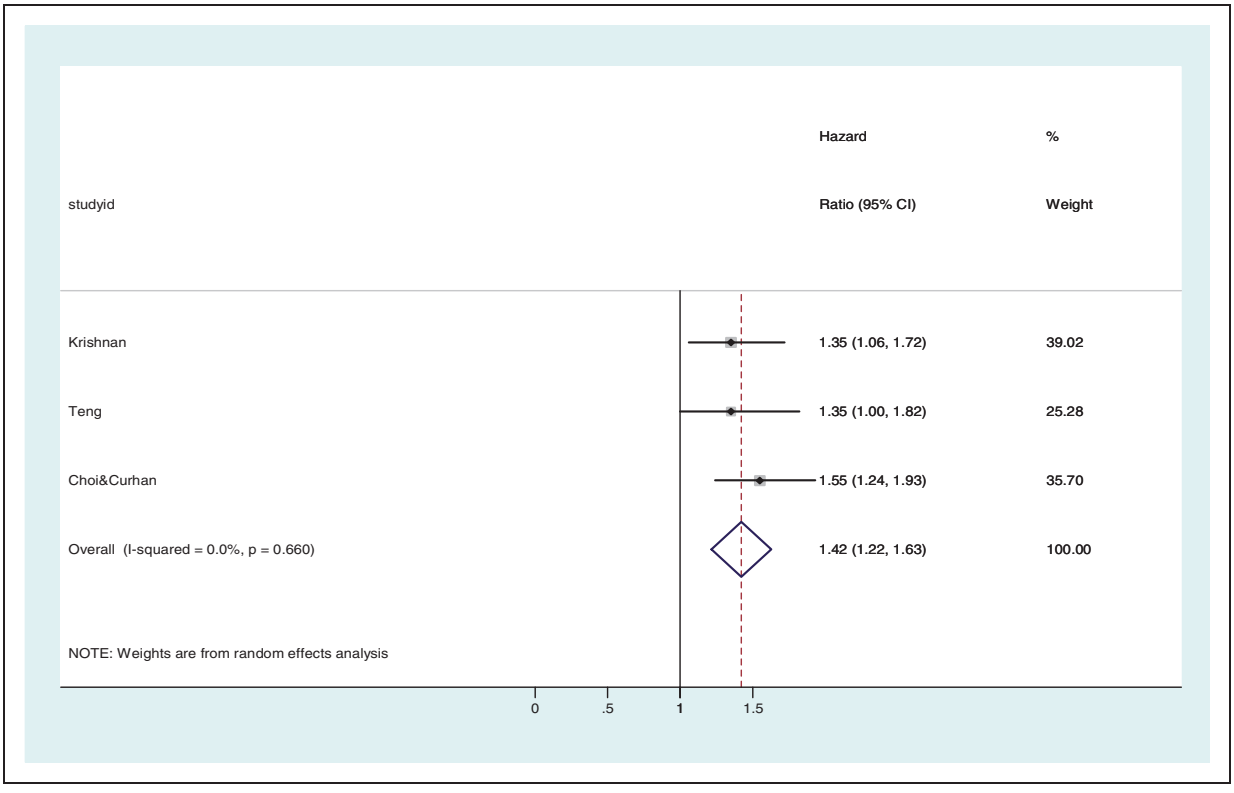

Figure 3. Meta-analysis of adjusted findings of studies reporting mortality from coronary heart disease.

Three of the studies included in that review were included in this meta-analysis;[11,12,20] however, one was excluded[24] as the study population consisted of renal dialysis and transplantation patients, and was not felt to be broadly representative of, or comparable with, the wider gout population, and impaired renal function is itself acknowledged to increase risk of cardiovascular mortality.[25,26] One more recent study was included in our review.[21] Our systematic review builds on the previously published work by conducting the first meta-analysis determining the excess risk of cardiovascular mortality associated with gout.

The precise relationship between gout and CVD remains unclear. The persistence of excess risk of cardiovascular and CHD mortality associated with gout in the pooled multivariate analysis, even after adjustment for traditional vascular risk factors, would suggest there are other important factors which influence this relationship. It is possible that this association is an indirect one, and simply an extension of the increased risk of CVD conferred by hyperuricaemia.[3] This occurs through a mechanism of amplified oxidation of lipids and induction of cellular oxidative stress which contributes to endothelial dysfunction, resulting in decreased arterial compliance, impaired blood flow, and a proatherogenic state.[27] However, since few studies include data on uric acid levels, we are unable to explore this further. Studies have also demonstrated renovascular disease, renal injury, and hypertension can result from this hyperuricaemic-mediated endothelial dysfunction,[28] further contributing to cardiovascular risk. Uric acid is also thought to have direct proinflammatory effects on vascular cells,[29,30] with evidence that reduction of uric acid levels reduces cardiovascular risk.[31] Allopurinol, the most commonly used urate-lowering therapy, has been shown to improve endothelial dysfunction,[32,33] blood pressure,[32,34] and exercise tolerance in patients with chronic stable angina.[35]

However, given that other inflammatory arthritides, such as rheumatoid arthritis and ankylosing spondylitis, not associated with hyperuricaemia also confer increased cardiovascular risk,[4,5] it would seem likely that the relationship is more complex. Common pathways of accelerated atherosclerosis resulting from endothelial dysfunction and impaired arterial compliance, as well as autoimmune inflammatory mechanisms involving proinflammatory cytokines such as tumour necrosis factor α and interleukins 1 and 6, by which inflammatory arthritides increase cardiovascular risk, have been suggested, and inflammatory activity is felt to be the major risk factor for the development of subsequent vascular disease.[36] Monosodium urate crystals deposited in gout have been shown to strongly induce inflammation in humans, through direct neutrophil activation and activation of the NALP3 inflammasome resulting in the release of similar proinflammatory cytokines, during an acute attack.[28] There is growing evidence that this inflammation persists between attacks,[37] with recent ultrasound studies demonstrating the presence of inflammation and synovitis in the intercritical period.[9,38] This recent literature has confirmed that gout should be considered a chronic inflammatory joint disease, and therefore, the possibility that persistent inflammation is one mechanism for increased burden of vascular disease in both gout and rheumatoid arthritis. The effect of inflammation on CVD has prompted the European League Against Rheumatism (EULAR) to publish recommendations for cardiovascular screening and management in both rheumatoid arthritis and gout patients,[39,40] including an aggressive approach to managing both risk factors and inflammatory burden.

However, the reasons for the absence of a similar association with mortality from MI remain unclear. This difference may reflect the presence of alternative underlying factors in the pathogenesis of MI when compared with other forms of CHD. Evidence suggests that coronary artery morphology is the most important factor differentiating patients who experience angina, compared to those with MI.[41] It may also reflect misclassification bias where, in the absence of post-mortem examination, cause of death is recorded as CHD or CVD rather than specifically MI. It may also result from surveillance bias, whereby diagnosis of gout and subsequent monitoring lead to increased likelihood of detection and management of CHD, and better education of patients about the need for prompt medical attention at the onset of symptoms to prevent progression to MI. However, it may simply be that further studies are required to investigate this particular relationship.

The limitations of our review include the small number of papers available for inclusion. However, each of these studies uses a large study population and, combined, the number of patients included in this meta-analysis exceeds 220,000. Moreover, by undertaking the meta-analysis in a stepwise fashion, pooling the studies one-by-one in chronological order, the pooled HR was not significantly altered from the HR reported in the first paper (published in 2007) after the addition of any of the later papers.

Despite a comprehensive search strategy, the possibility remains that some relevant articles may not have been identified. Similarly, papers with negative findings are less likely to be published, although there was no significant indication of publication bias from Begg's and Egger's tests. However, it must be acknowledged that Begg's and Egger's tests have low power to detect biases where study numbers are small.[42]

There was some heterogeneity between papers in the definitions of gout cases and the vascular risk factors included in the multivariate analyses, and unmeasured confounding must be considered given the observational nature of the included studies. Misclassification bias may also occur where studies relied upon diagnostic codes or death certificates to define outcomes.

The strengths of our review are that only large cohort studies are included, with participants being free of CVD at baseline. Data extraction and thorough methodological quality assessment was undertaken by two reviewers independently. Crude and multivariate data were pooled separately and potential sources of heterogeneity examined. Finally, no evidence of publication bias was found in our review.

In conclusion, whilst observational studies cannot demonstrate causation, this meta-analysis of large, high-quality cohort studies strongly supports gout as an independent risk factor for mortality from CVD and CHD. Current evidence does not support such an association with MI. The clinical implications of this review are the need to promote identification and management of cardiovascular risk factors in patients with gout, but also to identify and optimally manage gout in patients at risk of CVD. Further research will be required to establish whether the optimal management of gout, or the aggressive management of cardiovascular risk factors reduces negative outcomes for these patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

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EXTENDED REPORT

Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK Clinical Practice Research Datalink

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ABSTRACT

Objectives To determine whether gout increases risk of incident coronary heart disease (CHD), cerebrovascular (CVD) and peripheral vascular disease (PVD) in a large cohort of primary care patients with gout, since there have been no such large studies in primary care.

Methods A retrospective cohort study was performed using data from the Clinical Practice Research Datalink (CPRD). Risk of incident CHD, CVD and PVD was compared in 8386 patients with an incident diagnosis of gout, and 39 766 age, sex and registered general practice-matched controls, all aged over 50 years and with no prior vascular history, in the 10 years following incidence of gout, or matched index date (baseline). Multivariable Cox Regression was used to estimate HRs and covariates included sex and baseline measures of age, Body Mass Index, smoking, alcohol consumption, Charlson comorbidity index, history of hypertension, hyperlipidaemia, chronic kidney disease, statin use and aspirin use.

Results Multivariable analysis showed men were at increased risk of any vascular event (HRs (95% CIs)) HR 1.06 (1.01 to 1.12), any CHD HR 1.08 (1.01 to 1.15) and PVD HR 1.18 (1.01 to 1.38), while women were at increased risk of any vascular event, HR 1.25 (1.15 to 1.35), any CHD HR 1.25 (1.12 to 1.39), and PVD 1.89 (1.50 to 2.38)) but not any CVD.

Conclusions In this cohort of over 50s with gout, female patients with gout were at greatest risk of incident vascular events, even after adjustment for vascular risk factors, despite a higher prevalence of both gout and vascular disease in men. Further research is required to establish the reason for this sex difference.

INTRODUCTION

Gout is the most prevalent inflammatory arthritis, affecting an estimated 2.5% of the population in the UK,[1] and 3.9% in North America.[2] It is associated with elevated levels of serum uric acid (SUA) and deposition of monosodium urate crystals in tissues and joints, leading to excruciating painful attacks of peripheral joint synovitis which, in the UK, are largely managed in primary care by general practitioners (GP) who refer on for specialised care only if necessary.

Hyperuricaemia, the biochemical precursor to gout, has been linked with an increased incidence of, and mortality from, both CHD and stroke.[3 4] Although gout is traditionally thought of as an intermittent inflammatory condition, recent ultrasound studies have identified persistent subclinical inflammation in the intercritical period between acute attacks.[5] It has been hypothesised that the combination of persistent inflammation and hyperuricaemia may potentiate or synergise CHD development.[6] Deposition of urate crystal material in vessel walls has been proposed to cause neutrophil and platelet activation and release of inflammatory mediators that promote cardiovascular damage.[7–9]

Epidemiological studies examining the relationship between gout and CHD report conflicting findings, with a significant association reported by some,[10–13] but not others,[14–16] and investigations of risk of cerebrovascular disease (CVD) or peripheral vascular disease (PVD) in patients with gout comparatively fewer.[16–18] Consequently, the risk intrinsic to gout itself, compared to that from hyperuricaemia or vascular risk factors, such as hypertension and obesity commonly found in patients with gout, remains unclear. Additionally, many of these studies have been conducted in secondary care populations, who may be characterised by more severe disease, rather than primary care where the majority of patients with gout are managed.[19]

The use of data from routinely collected primary care records is accepted as a cost-effective way to undertake epidemiological studies of large patient populations across a broad population spread.[20] The UK Clinical Practice Research Datalink (CPRD) is the largest database of electronic primary care health records (EHR) in the world, and has previously been used in the study of the association of inflammatory conditions and vascular disease,[21 22] as well as in the epidemiology of gout.[1 23]

We sought to investigate the association between gout and incident CHD, CVD and PVD in a large sample of the UK general practice population.

METHODS

Clinical practice research datalink

The UK CPRD contains data for approximately 9% of the UK population. Currently, 650 general practices contribute high-quality data with over 5.5 million active patients,[24] thought to be broadly representative of the general UK population,[24 25] and high validity of diagnosis in the CPRD has been reported.[26 27]

Participant identification

Patients consulting in primary care between 1987 and 1999, with an incident diagnosis of gout, were identified. Potential control subjects with no history

of gout were stratified by general practice, year of birth and sex, and up to five were randomly selected from the appropriate stratum for each patient with gout. Baseline for patients with gout was considered to be the first entry of a diagnostic code for gout in their EHR, and for patients without gout the date of diagnosis of gout in their matched gout patient. Pre-baseline EHRs were searched for codes relating to prescriptions for colchicine or urate-lowering therapy, and where these were present, the patient record was individually examined to determine whether a prior diagnosis of gout was probable, and subsequent inclusion or exclusion.

Participants in both cohorts were required to be aged over 50 years at baseline, since vascular events themselves are rare under the age of 50 years, and are often influenced by other underlying factors which may be difficult to account for. Patients with a previous history of vascular disease were excluded in order to minimise the surveillance bias associated with follow-up for a previous event, and remove the contribution of additional risk conferred by a previous event.

Outcome measures

Outcomes of interest were time to first recording of CHD, CVD and PVD within the patient's EHR. Events of interest were angina, myocardial infarction (MI) and any CHD (including angina, MI and all less specific codes describing incident coronary heart disease), stroke/cerebrovascular accident (CVA), transient ischaemic attack (TIA) and any CVD (including TIA, CVA and all less specific codes describing incident cerebrovascular events) and PVD (considered to be any narrowing of arteries distal to the arch of the aorta and identified in the EHR using codes associated with symptoms at incidence of disease, eg, intermittent claudication, or asymptomatic identification by screening in high-risk populations, eg, diabetics). The term 'any vascular event' was used to describe overall risk of developing any of these outcomes of interest. Due to the nature of the coding, we were not able to separate ischaemic from haemorrhagic cerebrovascular events, and for this reason they were considered together. A list of Read Codes used is available on request. Participants were followed from baseline until they experienced an event of interest, or in those who remained event-free, until the occurrence of death, transfer away from the practice contributing their records to the CPRD, last collection of records from the practice by the CPRD, or 10 years from baseline, whichever was the earliest.

Vascular risk factors

Potential explanatory covariates were chosen by consensus between GPs and rheumatologists, to represent traditional risk factors for vascular diseases, well described in the literature, and used in previous studies of vascular disease.[10–12 14] Baseline data on presence of hypertension, hyperlipidaemia, chronic kidney disease, Body Mass Index (BMI), ever/never exposure to alcohol, smoking, statins and aspirin were identified for all participants from their EHR using relevant Read Codes. Smoking and alcohol data were entered as categorical variables, (ever/never exposure or missing) in order to minimise the effect that missing data in the recording of these covariates would have on the size of the dataset available for analysis. Charlson Co-morbidity Index[28] at baseline was also calculated using a technique described by Khan *et al*.[29] This index is calculated based upon the presence or absence of 19 weighted comorbid conditions, including history of diabetes which was, therefore, not separately included in the multivariate analysis. Physical activity and family history of vascular disease were not included in the multivariable analysis due to high levels of missing data, and hyperuricaemia could not be included since SUA is not routinely measured in non-gout patients in the UK.

Statistical analysis

Descriptive statistics were used to describe the baseline demographics of the sample. Cox proportional hazard modelling was used to produce both unadjusted and adjusted HRs, estimating the excess risk of the various forms of vascular disease, associated with gout,[30] using robust SEs to adjust for any clustering induced by matching.[31] The validity of the proportional hazards assumption was tested using Schoenfeld residuals and Stata's own diagnostic test. Where this assumption was violated, suggesting the risk associated with potential explanatory covariates may vary over time, the relevant variables were reintroduced into the model as time-varying covariates.[32]

Baseline age, BMI, smoking and alcohol exposure and Charlson comorbidity index, along with sex and gout×sex interaction were introduced into the first model for analysis (Model 1), in order to minimise surveillance bias and represent a typical patient with gout presenting to a GP for the first time. Additionally, the second model also included baseline history of hypertension, hyperlipidaemia, chronic kidney disease and exposure to prescription statins and aspirin.

The association with vascular events was investigated by sex subset. The interaction between gout and sex was tested, with significance assessed using the Wald test, since robust SEs were used. Stratified effect sizes were calculated in order to clarify sex differences, using the STATA LINCOM command to calculate the appropriate linear combinations from the model containing the interaction. This has the added advantage of using all the data rather than fitting separate models for sex.[33] Data were analysed using Stata statistical software release 12 (StataCorp: College Station, TX, 2011).

This study protocol received approval from the Independent Scientific Advisory Committee for the Medicines and Healthcare products Regulatory Agency Database Research (reference number 10_109)

RESULTS

A total of 8386 patients with gout were age, sex and practice-matched to 39 766 participants without gout. Mean age at diagnosis for patients with gout was 66.3 years (SD 10.8), and 69.4% were male. Patients with gout had an increased prevalence of all risk factors of interest at baseline, with the exception of diabetes mellitus, when compared with non-gout patients (table 1).

The proportional hazards assumption for gout exposure was met for all types of vascular events. The time-varying covariates entered for each outcome are available in the online supplementary table S1.

A statistically significant interaction between gout and sex was found, and for this reason, the results are presented by sex. The details of the interaction in the gout effect between men and women are available in the online supplementary table S2.

Totally, 11 266 vascular events occurred during the follow-up (table 2). Absolute risk of any vascular event per 1000 person years in men with gout was 43.63 (41.55 to 45.77) compared to 33.70 (32.86 to 34.55) in men without gout, corresponding to a crude HR of 1.29 (1.22 to 1.36), and in women with gout it was 51.89 (48.32 to 55.64) compared to 33.41 (32.15 to 34.71), corresponding to a HR of 1.56 (1.44 to 1.69). The most marked increase was in risk of PVD in women, where absolute risk more than doubled, from 3.05 (2.68 to 3.46) to 7.09 (5.81 to 8.55) events per 1000 person-years in women

Table 1 Participant demographics at baseline

	Gout	Non-gout	p For significance
Participants, n	8386	39 766	
Age at diagnosis, years	66.3 (±10.8)	66.2 (±10.7)	0.99
Male, %	69.4	69.2	0.70
Ever smoker (missing), %	28.3 (23.1)	26.2 (31.2)	<0.01
Ever drinker (missing), %	73.5 (13.8)	64.4 (21.2)	<0.01
BMI >25 kg/m^2 (missing),%	59.7 (18.3)	43.6 (25.0)	<0.01
Hypertension, %	36.0	17.3	<0.01
Hyperlipidaemia, %	5.7	3.2	<0.01
Diabetes, %	4.2	4.4	0.33
Chronic kidney disease, %	1.4	0.2	<0.01
Ever statin use, %	34.3	25.6	<0.01
Ever aspirin use, %	42.7	33.4	<0.01

BMI, Body Mass Index

with gout, corresponding to an unadjusted HR of 2.35 (1.87 to 2.94). There was a statistically significant increased risk of all vascular outcomes for women with gout, with the exception of MI, and for men with gout except any CVD and CVA (table 2).

In both sexes, previously identified risks remained significant, but were attenuated after adjustment for the vascular risk factors included in model 1 (table 3).

After adjustment for the extended range of covariates included in model 2, a clear sex difference emerged. Gout was an independent risk factor for any vascular event, any CHD and PVD, but not for any of the other vascular outcomes of interest for men. However, gout remained an independent risk factor for all types of vascular diseases in women except MI and any CVD (table 3) and, additionally, the magnitude of risk of all outcomes was found to be greater in women.

DISCUSSION

This study provides evidence that patients of both sexes with gout are at increased risk of any vascular events, any CHD and PVD even after adjustment for traditional vascular risk factors, but the magnitude of this risk is greater in women. Additionally, female gout patients are at increased risk of angina, TIA and CVA, but male patients with gout are not.

While our recent meta-analysis demonstrated an increased risk of mortality from cardiovascular causes,[34] meta-analysis of risk of incident cardiovascular disease in gout has not been undertaken to date. Previous studies examining the association between gout and incident CHD have been conflicting; adjusted results from the Framingham study reported an increased incidence of CHD and angina in men but not women, but both a prospective study on male health professionals from the USA and a primary care case-control study using patients of both sexes with gout from The Netherlands, reported no increased incidence of CHD.[10 14 15] Studies of the association between gout and MI produce similar conflicting reports. Krishnan *et al*,[11] report an increased incidence of non-fatal and all MI in a male cohort nested in a controlled trial examining the efficacy of coronary risk reduction in men at high risk of vascular disease, DeVera *et al*,[35] report an increased incidence of non-fatal and all MI in women, but not men in a retrospective cohort study in Canada, and no association between gout and MI in either sex reported by Abbott *et al*, 1988.[10]

The contradictory nature of current evidence may arise from significant heterogeneity of study design, and ascertainment of

Table 2 Unadjusted risk of vascular disease by sex

		Men			Women			
Outcome	Number of events	Gout Absolute risk per 1000 person-years (95% CI)	Non-gout Absolute risk per 1000 person-years (95% CI)	Gout vs non-gout HR (95% CI)	Gout Absolute risk per 1000 person-years (95% CI)	Non-gout Absolute risk per 1000 person-years (95% CI)	Gout vs non-gout HR (95% CI)	p For sex interaction
Any vascular	11 266	43.63 (41.55 to 45.77	33.70 (32.86 to 34.55)	1.29 (1.22 to 1.36)	51.89 (48.32 to 55.64)	33.41 (32.15 to 34.71)	1.56 (1.44 to 1.69)	<0.01
Any CHD	6751	28.46 (26.80 to 30.20	21.06 (20.41 to 21.74)	1.36 (1.27 to 1.45)	29.11 (26.47 to 31.94)	17.72 (16.81 to 18.67)	1.64 (1.48 to 1.82)	<0.01
Angina	2862	11.80 (10.73 to 12.97)	8.95 (8.52 to 9.39)	1.31 (1.18 to 1.46)	12.32 (10.63 to 14.22)	7.23 (6.65 to 7.84)	1.70 (1.45 to 2.00)	<0.01
MI	2133	9.27 (8.34 to 10.29)	6.92 (6.55 to 7.31)	1.33 (1.18 to 1.50)	6.11 (4.93 to 7.48)	5.19 (4.70 to 5.72)	1.19 (0.95 to 1.49)	0.39
Any CVD	2208	13.09 (11.98 to 14.28)	11.13 (10.66 to 11.63)	1.11 (0.97 to 1.26)	20.78 (18.55 to 23.19)	14.54 (13.72 to 15.41)	1.39 (1.18 to 1.65)	0.04
TIA	1733	6.04 (5.27 to 6.87)	4.77 (4.46 to 5.10)	1.25 (1.09 to 1.45)	9.34 (7.87 to 11.00)	6.06 (5.53 to 6.62)	1.57 (1.30 to 1.89)	0.07
CVA	2386	7.45 (6.62 to 8.38)	6.63 (6.26 to 7.02)	1.12 (0.98 to 1.27)	13.71 (11.92 to 15.09)	8.39 (7.77 to 9.05)	1.67 (1.43 to 1.95)	<0.01
PVD	1300	5.60 (4.88 to 6.41)	4.01 (3.72 to 4.31)	1.39 (1.19 to 1.62)	7.09 (5.81 to 8.55)	3.05 (2.68 to 3.46)	2.35 (1.87 to 2.94)	<0.01

Covariates include age at baseline, sex, gout×sex interaction.
CHD, coronary heart disease; CVA, cerebrovascular attack; CVD, cerebrovascular disease; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Table 3 Adjusted risk of vascular disease by sex

	Model 1			Model 2		
Outcome	HR men (95% CI)	HR women (95% CI)	p For sex interaction	HR men (95% CI)	HR women (95% CI)	p For sex interaction
Any vascular	1.22 (1.16 to 1.29)	1.45 (1.34 to 1.57)	<0.001	1.06 (1.01 to 1.12)	1.25 (1.15 to 1.35)	<0.001
Any CHD	1.26 (1.18 to 1.35)	1.50 (1.35 to 1.67)	0.005	1.08 (1.01 to 1.15)	1.25 (1.12 to 1.39)	0.024
Angina	1.20 (1.08 to 1.34)	1.55 (1.32 to 1.82)	0.010	1.02 (0.92 to 1.13)	1.28 (1.09 to 1.51)	0.003
MI	1.30 (1.15 to 1.46)	1.12 (0.89 to 1.40)	0.254	1.12 (1.00 to 1.27)	0.97 (0.77 to 1.22)	0.263
Any CVD	1.11 (0.97 to 1.26)	1.35 (1.14 to 1.60)	0.068	0.95 (0.83 to 1.09)	1.17 (0.99 to 1.38)	0.058
TIA	1.22 (1.05 to 1.41)	1.50 (1.24 to 1.81)	0.085	1.02 (0.88 to 1.18)	1.26 (1.05 to 1.53)	0.796
CVA	1.08 (0.95 to 1.23)	1.58 (1.35 to 1.84)	<0.001	0.93 (0.81 to 1.06)	1.34 (1.15 to 1.57)	<0.001
PVD	1.35 (1.16 to 1.58)	2.17 (1.73 to 2.73)	<0.001	1.18 (1.01 to 1.38)	1.89 (1.50 to 2.38)	0.04

Model 1 covariates: sex, gout×sex interaction, baseline age, Body Mass Index >25 kg/m^2, ever/never smoking, ever/never alcohol consumption, Charlson Comorbidity Score.
Model 2 covariates include Model 1 and baseline history of hypertension, hyperlipidaemia, chronic kidney disease, ever/never statin use, ever/never aspirin use.
CHD, coronary heart disease; CVA, cerebrovascular attack; CVD, cerebrovascular disease; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

gout, choice of potential explanatory covariates and study populations used, all of which (with the exception of one[35]) are of smaller size than that used here, and some of which are specialised (e.g. health professionals),[12 14] or solely male.[11 12 14]

The findings of increased risk of vascular disease in females are consistent with those of two previous studies.[16 35] The reasons for this increased risk remain unclear, but prolonged exposure to hyperuricaemia prior to the onset of clinical gout may play a role, since women have been observed to have an older mean age at onset of gout, lower mean SUA levels, and reduced risk of incident gout compared with men with a comparable level of hyperuricaemia.[36–38] This prolonged exposure may be lengthened further if clinicians are less vigilant for gout in women, potentially delaying diagnosis and increasing crystal and inflammatory burden. Incidence of gout is higher in postmenopausal women,[39] suggesting that oestrogen is an important influence, both on renal urate handling, and also on the increased incidence of abdominal obesity and associated hyperinsulinaemia after menopause which further impairs renal excretion of urate.[38] A stronger multiplicative effect between hyperuricaemia and metabolic vascular risk factors resulting in a higher propensity of women to hyperuricaemia-induced microvascular damage has also been suggested.[40] However, there may simply be less aggressive management of vascular risk factors or gout itself in female primary care patients. Although there was a statistically significant difference between the proportions of male and female patients with gout prescribed allopurinol (43% vs 39%, p<0.01 for difference) in our sample, a difference of this magnitude is unlikely to fully explain the sex differences seen, and further research is required in order to elucidate the nature of this relationship.

The increased incidence of PVD found in patients of both sexes with gout is also in line with the only other study to have examined this relationship.[17] This association may result from common risk factors shared by gout and PVD, such as hypertension, and chronic kidney disease,[41] but further research is needed to investigate this.

Our findings have several important implications for clinical practice. First, current evidence suggests that the clinical management of gout in primary care is suboptimal,[1 42] despite approximately 1 in 40 people in the UK, and over 8 million people in the USA currently affected.[1 2] Thus, even a small increase in vascular risk will give rise to a substantial number of new vascular events. Since there is evidence that cardiovascular disease in patients with gout often goes unrecognised and undertreated in primary care, with only a quarter of people consulting with acute gout screened for cardiovascular risk factors within the subsequent month,[43] despite both national and international guidance recommending this,[44–46] the results of this study suggest a substantial need to change practice. Second, both gout and vascular disease have historically been considered diseases of men, and so even in that minority of patients who are screened for vascular risk factors, those chosen may not be those most at risk, and since this study highlights the most serious consequences for women, perhaps more attention should be paid to prompt and reliable diagnosis of gout, followed by optimal management in female patients, including serious consideration of vascular risk reduction.

Third, screening for PVD in patients with gout is not currently recommended as part of best practice. The increased risk of incident PVD was present in both sexes, and was the strongest of those we identified. There is evidence that 44% of patients screened for PVD had PVD without evidence of CHD,[47] suggesting that this may not have been detected by routine practice in primary care, even by those adhering to current guidance on cardiovascular screening in gout, and suggesting the need for a change in recommendations to include screening for PVD.

This study has a number of strengths compared with existing literature. The use of a large number of well-validated primary care EHR means the study is generalisable to the wider population of patients with gout. Additionally, matching patients by age, sex and GP practice reduces the risk of sociodemographic confounding. Moreover, the exclusion of patients with a prior history of vascular events reduces both surveillance bias and the additional risk conferred by a vascular history, allowing the contribution of gout itself to be more accurately investigated.

The limitations of this study include possible misclassification bias from the use of diagnostic codes to define either gout, based upon primary care diagnosis usually made on clinical grounds, or CHD/CVD outcomes of interest, where terminology may have changed over time or generalised codes may have been used. Previous studies indicate reasonable validity of gout diagnosis in primary care.[42 43] and other studies undertaken in the CPRD have selected gout cases using a primary care diagnosis.[1 23 48] Similarly, a recent review of validity of diagnoses in CPRD reported a positive predictive value of diagnosis of MI coded in CPRD of over 80%, with comparable reliability of coding for ischaemic heart disease to other primary care databases,[26] although literature on identification of vascular diseases in EHR databases is sparse.

While multiple adjustments on risk factors for vascular events have been performed to take into account differences between exposed and unexposed groups, we cannot rule out residual confounding effects. Similarly, while matching by registered general practice is an accepted method of accounting for socio-demographic differences, there may be considerable sociodemographic variation within a practice area that may influence this relationship. Furthermore, we were unable to adjust for hyperuricaemia (since SUA is not routinely measured in patients without gout in the UK) and family history of vascular disease and levels of physical activity in our analysis (due to poor levels of recording), which may have some bearing on this relationship. However, some degree of the effect of the variables we were unable to account for is likely to be reflected in the other risk factors included, for example, physical activity and BMI.

In conclusion, this study suggests an association between gout and subsequent CHD and PVD in both sexes, independent of traditional vascular risk factors. These risks are greatest in women, and a particularly strong association between gout and incident PVD in both sexes was found. Further work is required to establish the effect of optimum management of both vascular risk factors and gout itself on the long-term health of gout patients, clarify the nature of the relationship between gout and PVD, and the mechanism by which women are at greatest risk.

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Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK Clinical Practice Research Datalink

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Notes